Palliative care-related problems in the first three months following HIV diagnosis in East Africa
a longitudinal study

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Palliative care-related problems in the first three months following HIV diagnosis in East Africa: a longitudinal study

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Abstract

Background

HIV policy states that palliative care is required from diagnosis onward, but evidence of the prevalence, severity and duration of patient-centred problems at HIV diagnosis is very limited, particularly in Africa. This thesis aims to determine palliative care-related problems reported by outpatients over three months from diagnosis, taking a patient-centred approach.

Methods

A prospective observational cohort was conducted in Kenya and Uganda. Twelve HIV facilities each consecutively recruited 100 adults and those diagnosed within 14 days previously were selected. Outcomes were the seven patient-response items of the APCA African POS, a validated instrument completed at four monthly intervals. Cross-sectional analysis used ordinal logistic regression (cross-sectional multivariate), proportion of net change (longitudinal univariate) and population-averaged fixed-effects conditional logistic regression (longitudinal multivariate).

Results

Among 438 participants (aged 18-59, 67% women), problems are highly prevalent at diagnosis (47% received no help and advice, 11% severe worry, 6% severe pain). Problems decrease over time on average but many persist after three months (e.g. 28% unable to share feelings). Physical problems decrease most rapidly, psychosocial more slowly. Poverty is a risk factor for pain, symptoms and difficulty finding life worthwhile(OR=0.8-0.9). Five outcomes are exacerbated by limited physical function(OR=1.6-3.1) but none are associated with CD4 count. Uniquely, difficulty sharing feelings is more common over time for those with full physical function (OR=0.7) and the highest relative wealth(OR=1.2). Psychosocial and spiritual problems are more severe in Uganda (OR=2.7-3.3). Patients taking

antiretroviral therapy have fewer symptoms, more peace, and more help/advice(OR=0.6=0.7).

Conclusion

This thesis presents the highest quality evidence of patient-reported problems at HIV diagnosis. Physical, psychological, social and spiritual problems are common and severe, requiring holistic assessment and management. The findings are relevant to service development in the context of scaled-up testing services for access to antiretroviral therapy. Staff need palliative care training, with support from specialist centres for intractable problems. This research contributes longitudinal analysis techniques appropriate for resource-limited settings, helping overcome research barriers.

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Publications and presentations

Research publications in peer-reviewed journals

Simms V, Harding R, Higginson IJ (2011). What palliative care-related problems do patients experience at HIV diagnosis? A systematic review of the evidence. Journal of Pain and Symptom Management. Epublished 25 May. PMID: 21620647

Harding R, Simms V, Penfold S, McCrone P, Moreland S, Downing J et al (2010). Multi-centre mixed- methods PEPFAR HIV care & support public health evaluation: study protocol. BMC Public Health **10**:584. PMID: 20920241

Published research abstracts

Simms V, Harding R, Namisango E, Penfold S, Nusbuga C, Kataike J et al (2009). What are the palliative care needs of adults newly diagnosed with HIV in Uganda? A multicentre study. 11th Congress of the European Association for Palliative Care. Vienna, Austria (7-10 May)

Other presented abstracts

Simms V, Namisango E, Penfold S, Downing J, Powell RA, PEPFAR Care and Support PHE Research Team et al (2010). Multidimensional palliative care-related problems in the first three months with an HIV diagnosis: a longitudinal cohort study in Kenya and Uganda. 3rd African Palliative Care Association Conference. Windhoek, Namibia (15-17 September)

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Simms V, Harding R, Higginson IJ (2010). Palliative care problems at HIV diagnosis are severe and under-researched: a systematic review. XVIII International AIDS Conference. Vienna, Austria (19-23 July)

Simms V, Harding R, Penfold S, Powell RA, Downing J, Namisango E et al (2010). Quality of life improves after HIV diagnosis, but ART is not the cause: a multicentre longitudinal study in Kenya and Uganda. XVIII International AIDS Conference. Vienna, Austria (19-23 July)

Simms V, Penfold S, Namisango E, Downing J, Higginson IJ, Harding R (2009). At HIV diagnosis, patients with no accompanying carer have extra palliative care burden: a multicentre East African study. Palliative Care Research Society, Annual Scientific Meeting. London, UK (12 November)

Abbreviations

General abbreviations

ADL	Activities of daily living
AIDS	Acquired immune deficiency syndrome
APCA	African Palliative Care Association
ART	Antiretroviral therapy
CTX	Cotrimoxazole
DALY	Disability adjusted life year
Exp	Exponential
GEE	Generalised estimating equations
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
IDU	Injection drug user
KEMRI	Kenya Medical Research Institute
MSM	Men who have sex with men
NGO	Non-governmental organisation
OR	Odds ratio
PEPFAR	President's Emergency Plan for AIDS Relief
PHE	Public Health Evaluation
PTSD	Post traumatic stress disorder
QoL	Quality of life
RCT	Randomised controlled trial
RNA	Ribonucleic acid
SC	Seroconverter/seroconversion
STI	Sexually transmitted infection
TASO	The AIDS Support Organisation
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNCST	Uganda National Council for Science and Technology
USAID	United Stated Agency for International Development
VAS	Visual Assessment Scale
VCT	Voluntary counselling and testing
WHO	World Health Organisation

Questionnaires

BDI	Beck Depression Inventory
BSI	Brief Symptom Inventory
CES-R	Centre for Epidemiological Studies - Depression
CSRI	Client Services Receipt Inventory
ECOG	Eastern Cooperative Oncology Group global performance scale
HADS	Hospital Anxiety and Depression Scale
HRDS	Hamilton Rating Depression Scale
IES	Impact of Events Scale
MINI	Mini International Neuropsychiatric Interview
MOS-HIV	Medical Outcomes Scale – HIV version
MOS-SF	Medical Outcomes Scale – Short Form
MSAS-SF	Memorial Symptom Assessment Scale-Short Form
POMS	Profile Of Mood States
POS	Palliative Outcome Scale
QL-Index	Quality of Life Index
SC-90	Symptom Checklist-90
SRS	Social Relationship Scales
SSC-HIVrev	Revised Sign and Symptom Checklist for Persons With HIV Disease
STAI	State/Trait Anxiety Inventory

My contributions to this thesis

The data used in this thesis were collected for a longitudinal quantitative study as part of Phase 2 of a Public Health Evaluation (PHE) of the Care & Support activities of the President's Emergency Plan for AIDS Relief (PEPFAR), which was conducted in Kenya and Uganda. I was employed on this project for a year before beginning my PhD, and my contributions are detailed below. I contributed to many aspects of the study design and I was heavily involved in its execution.

The original concept of the PhD thesis was mine. I developed the aim, objectives and research questions, and conducted the systematic review. I identified the subsample of newly diagnosed participants from the total sample of quantitative data in the PHE, wrote the analysis plan and carried out all the analysis. All interpretations and conclusions are my own.

My contributions to Phase 2 of the PHE were:

Study design

I was involved in the study design discussions. I designed the sampling method for selection of Phase 2 sites and contributed to the selection of the outcome instruments.

Questionnaire pack design and layout

I led the design of the demography tool and the modification of the CSRI, incorporating other people's contributions. The APCA African POS and MOS-HIV were pre-existing instruments. I converted them into a format that was compatible with the database and easy for health care staff to complete. The questionnaire pack was piloted and modified, and has proved successful with a very low error rate.

Ethics clearance

I wrote the applications to King's College Research Ethics Committee, the Kenya Medical Research Institute (KEMRI) and the Uganda National Council on Science and Technology (UNCST), and obtained approval from all three.

Training

The data were collected by health care workers (HCWs) trained and supervised by research assistants who in turn were trained and supervised by myself and my colleagues. I was responsible for writing a manual and training research assistants in Uganda and Kenya in the use of EpiData and the principles of double entry and validation. As well as writing the programme for data management training, I also worked on the manuals for training of HCWs who would collect the data, and research assistants who would support them. I ran a five-day course in Kenya including training of trainers, and conducted seminars on a similar course in Uganda.

Data management

I designed a preformatted database with consistency checks using EpiData 3.1, ensuring that data could be entered safely at a distance. Throughout the study I received regular reports from the field, monitored data accuracy and managed problems from day to day.

Analysis

I contributed to the development of an analysis plan, with help from professor Peter Fayers and colleagues. I conducted the majority of descriptive analysis and all the multilevel modelling on the complete datasets, and presented the results in the form of graphs and tables, with interpretation.

Dissemination

I wrote the introduction, methods, longitudinal quantitative analysis, discussion and recommendations chapters for both the Uganda and Kenya Phase 2 reports, incorporating sections written by others and designing the finished product. In acknowledgement of this I am listed as the first author of the Uganda report. I also wrote summary versions of both reports.

A Introduction

HIV is a life-limiting, progressive disease, for which there is currently no prospect of a cure. Worldwide 33 million people have HIV, two thirds of whom live in sub-Saharan Africa(1), and it is the sixth most common global cause of death(2).

Relative to the standard care of other diseases, HIV clinical care is frequently marked by holistic, patient-centred care and support in both high-income and low-income contexts, However, perhaps as a response to the magnitude of the epidemic, there is a trend in the published HIV research literature to adopt a disease-centred approach, and to measure risks and benefits at the level of the population rather than the individual, and with more emphasis on prevention than care(3). HIV research has arguably centred on disease-centred outcomes such as immune system markers, as a proxy for mortality.

The past 25 years have seen great advances in HIV treatment, and as a result, mortality and morbidity have been greatly reduced in areas where this treatment is accessible(4). Quality of life (QoL) gained importance as a secondary outcome of clinical trials(5, 6), but much of the research into patient-centred outcomes such as QoL appears to operate from a disease-centred paradigm which is distant from reported patient experience(7).

Palliative care takes a patient-centred approach to improving the lives of people with HIV and their families(8). Traditionally, palliative care was seen as applicable in the end stages of HIV and AIDS(9). Indications are emerging that multi-dimensional problems such as physical symptoms, pain, anxiety and depression, social isolation and spiritual distress, are prevalent throughout the HIV illness, not only at the end stages. Antiretroviral therapy (ART) may reduce disease burden for the individual patient but there is evidence it is not associated with symptom prevalence(10). The importance of palliative care throughout the disease trajectory, which has long been recognised in policy by global organisations including the World Health Organization(11) and UNAIDS(12), has been neglected in research and practice. As a result there is little information or evidence on which to base palliative care in the earlier stages of disease and specifically at HIV diagnosis.

Evidence is needed to inform patient-centred palliative care prior to and alongside ART. In particular, patient experience of HIV diagnosis and the immediate post-diagnosis period is very poorly understood.

Routine and regular HIV testing is encouraged in areas of high prevalence, as part of strategies for prevention and care. It is important to plan services to establish optimal care for this group, whose numbers are unrecorded, but known only to be large and growing. To this end, quality patient-centred care requires an understanding of the multidimensional problems and symptoms experienced by people newly diagnosed with HIV, and whether they abate or intensify over time.

The aim of this thesis was to determine the palliative care related problems experienced by adults in East Africa following diagnosis of HIV and how those problems changed over the subsequent months, taking a patient-centred perspective to diagnosis, in order to appraise policy and inform clinical care.

B Background

This chapter summarises the epidemiology and natural history of HIV, as currently understood. Existing evidence of the multidimensional symptoms and problems associated with living with HIV is critically appraised. The development of palliative care, and the evolution of a sub-discipline of HIV palliative care, is described in general and within Africa specifically. Reasons for the limited research base for HIV palliative care in Africa are outlined. Potential benefits of palliative care at HIV diagnosis are presented with policy recommendations.

B.1 Introduction to HIV

B.1.i Epidemiology of HIV

HIV is a major global public health issue, the sixth most common cause of death worldwide in 2004, and the fifth highest cause of morbidity and mortality measured in disability adjusted life years (DALYs)(2). At the end of 2009 around 33 million people were living with HIV, over 22 million of them in sub-Saharan Africa(1). Table B-1 shows that sub-Saharan Africa has an adult HIV prevalence five times higher than any other world region. In 2008 70% of new infections and 70% of deaths due to HIV took place in Africa(1).

Table B-1: HIV prevalence worldwide. Reproduced from UNAIDS 'AIDS Epidemic Update 2009' (1)

Region	People living with HIV, 10,000s (95% CIs)	New infections in 2008, 10,000s (95% CIs)	Deaths in 2008, 10,000s (95% CIs)	Adult HIV prevalence (95% CIs)
Sub-Saharan Africa	2240 (2080-2410)	190 (160-220)	140 (110 -170)	5.2% (4.9%-5.4%)
South and Southeast Asia	380 (340-430)	28 (24-32)	27 (22-31)	0.3% (0.2%-0.3%)
Latin America	200 (180-220)	17 (15-20)	7.7 (6.6-8.9)	0.6% (0.5%-0.6%)
Eastern Europe and Central Asia	150 (140-170)	11 (10-130)	8.7 (7.2-11.0)	0.7% (0.6%-0.8%)
North America	140 (120-160)	5.5 (3.6-6.1)	2.5 (2.0-3.1)	0.6% (0.5%-0.7%)
East Asia	85 (70-100)	7.5 (5.8-8.8)	5.9 (4.6-7.1)	<0.1%
Western and Central Europe	85 (71-97)	3.0 (2.3-3.5)	13 (10-15)	0.3% (0.2%-0.3%)
North Africa and Middle East	31 (25-38)	3.5 (2.4-4.6)	20 (15-25)	0.2% (<0.2%-0.3%)
Caribbean	24 (22-26)	2.0 (1.6-2.4)	1.2 (0.9-1.4)	1.0% (0.9%-1.1%)
Oceania	6 (5-7)	0.4 (0.3-0.5)	0.2 (0.1-0.3)	0.3% (<0.3%-0.4%)
World total	**3340 (3110-3580)**	**270 (240-300)**	**200 (170-240)**	**0.8% (<0.8%-0.8%)**

In 2008 approximately 2.7 million people worldwide were infected with HIV, in line with an ongoing decrease from the peak of 3.5 million infections in 1996(1). Following this, the number of deaths per year has also begun to fall slightly (2.0 million in 2008, down from 2.2 million in 2004). Advances in treatment have given people with HIV a longer life expectancy. As a result, the number of people living with HIV continues to rise although incidence and population prevalence are declining. Annual UNAIDS reports (1, 13-16) track the number of infections and deaths using epidemiological techniques including sentinel sites and representative surveys. Information on the number of people diagnosed with HIV is not collected or presented.

The end stage of HIV infection, AIDS, was first recognised as a new condition in the USA in 1981, as a cluster of unusual opportunistic infections in previously healthy gay men(17). Epidemiological research showed the cause was likely to be a blood-borne pathogen causing immune dysfunction, and within the next few years the virus was isolated and an antibody test developed. HIV is a retrovirus, meaning that its genetic code is stored as RNA rather than DNA. It preferentially infects lymphocytes, particularly the CD4 cell or helper T cell which coordinates immune response to infection.

The most common route of infection is via sexual transmission, followed by infection from mother to child, either across the placenta in pregnancy, at birth, or via breastfeeding(18). Blood transmission can take place by transfusion or shared injecting equipment. As a retrovirus, HIV is unstable, with a very high mutation rate. It is also fragile and cannot remain viable outside a host cell. Its rapid mutation, and its method of preferentially infecting those cells most equipped to combat it, make HIV enormously difficult to remove after infection. Despite three decades of research, no cure exists.

There are two main types of HIV: HIV-1, the most common, and HIV-2, a somewhat less virulent strain found primarily in West Africa(18). The most likely hypothesis is that HIV-1 is descended from a simian immunodeficiency virus (SIV) in the pygmy chimpanzee, the primate most closely related to humans, while HIV-2 appears to have developed from a virus of the sooty mangabey monkey. The genetic variation and rate of change in HIV suggest that each strain crossed the

species barrier into humans several times during the first half of the twentieth century. The earliest certain reference point is an HIV-positive blood sample taken in the Democratic Republic of Congo(DRC) in 1959(18). Its long dormancy period and highly variable expression prevented the recognition of AIDS as a disease until 1981, by which time HIV had reached 10% population prevalence in parts of Africa(19) and had spread around the world.

Epidemiological surveys have identified two patterns of HIV distribution. In sub-Saharan Africa the epidemic was generalised, with heterosexual transmission driving infections, and a slightly higher prevalence in women than men. In all other regions of the world the epidemic was concentrated into vulnerable populations; sex workers, injection drug users (IDU), men who had sex with men, and haemophiliacs. More detailed research has shown that this distinction between patterns was overly simplistic. HIV prevalence is higher than average among men who have sex with men in Zambia(15), while in China, heterosexual transmission has overtaken injections as the primary cause of new infections(1).

In Kenya and Uganda the HIV pandemic is generalised, or mature(14). HIV is highly prevalent throughout the population, a distribution found only in sub-Saharan Africa(15). The main route of infection is heterosexual sex, followed by vertical transmission. HIV is more prevalent among women than men(Table B-2).

Table B-2: Demographic characteristics of Kenya and Uganda(20-22)

	Uganda	**Kenya**
Median age	15 years	18.7 years
Mean life expectancy	52.7 years	57.9 years
People living with HIV (thousands)		
- **Men (15+)**	300-370	600-700
- **Women (15+)**	440-540	800-1,100
- **Children (0-14)**	120-150	130-180
Population size	32.4 million	39.0 million
GDP per capita (US$)	1300	1600
Below poverty line (%)	35	50
Urbanisation (% urban)	13	22

B.1.ii Natural history of HIV

HIV infection begins with a flu-like illness of variable severity and a spike in viral load (the concentration of virus in blood). Thereafter the presence of the virus is diminished to a very low level, and gradually rises over several years. Apart from the effects caused by HIV itself, immune system suppression leads to opportunistic infections caused by pre-existing pathogens as well as an increased susceptibility to infection by new ones.

Great advances in treatment have been achieved since the development of the first antiretroviral (ARV) drug in 1984. A leap forward was made in 1996 with the development of triple combination therapy, which suppresses viral load to undetectable levels. A collaboration of high-quality, long term cohort studies has shown that highly active antiretroviral therapy (HAART) halves mortality rate(4). It is said that HAART makes HIV into a chronic, manageable condition if ART is initiated early(23), although, according to current evidence from cohort studies, mortality remains higher than in the general population(24). An increasing proportion of people with HIV die prematurely from other causes such as liver disease, cancer and non-AIDS-defining infections(25), particularly in developed countries(26). In medical literature the term ‘AIDS’ is now used less frequently and is usually replaced by ‘HIV’, in recognition of the view that the illness comprises the whole period of HIV infection, and not only the end stage.

Progression of HIV is monitored by the number of CD4 cells per millilitre of blood, by the proportion of lymphocytes which are CD4 cells, and by viral load – number of RNA copies per millilitre of blood. The optimal time of ART initiation is a focus of research and debate(27). On the one hand HIV is progressive, and observational cohort studies have shown that mortality is higher if treatment is delayed until CD4 count falls below 200 and higher still below 100 or 50(28); on the other hand, ART has severe side effects and the utility of each drug for an individual is limited by the development of resistance. The point at which benefits outweigh costs is affected by the quality of current treatments and those which may be developed in the future. Recent WHO guidance raised the recommended threshold of ART initiation from 200 CD4 cells per ml to 350(29).

Treatment guidelines for ART initiation are based on observational cohort studies, as prospective trials with randomisation are not ethical for an intervention with the proven benefits of ART. The results of two large observational cohort collaborations were published in 2009. In North America, patients who began ART with a CD4 above 500 showed a 69% reduction in all-cause mortality compared to those with a CD4 count of 351-500(30). However, at the same time the When to Start Consortium in Europe found no association between CD4 count at initiation and mortality(31), after accounting for lead time bias (the fact that those with a lower CD4 count have been HIV positive for longer). In both studies, patients who began ART earlier than usually advised may have differed from the others in ways which could have biased the results.

The course of HIV disease is heavily influenced by the social environment, most obviously in availability and accessibility of ART, but also in the prevalence of other infectious diseases(32), nutritional security, and access to general medical care(33). Farmer calls into question the idea of a ‘natural history’ of HIV, and suggests that it has instead a biosocial history(33). This raises the issue of the extent to which research findings can be generalised across cultural and economic barriers, a problem in many health conditions.

B.1.iii Physical problems in HIV disease

At present, verifiable evidence of symptom prevalence in HIV is scant, and it is necessary to generalise across cultures and settings. A 2003 review of HIV palliative care in the era of ART presented the evidence of HIV symptom prevalence, derived from five studies based in Europe and North America(34). These populations largely consisted of people with advanced HIV and AIDS. The Selwyn review found consistent evidence of highly prevalent weight loss, anorexia, pain, cough, and fatigue(Table B-3). Diarrhoea, respiratory symptoms, nausea/ vomiting, and dry skin were also frequent. The extent of symptoms earlier in the course of infection were unknown. Even though the aim of the review was to discuss the role of palliative care in the era of ART, data collection predated the

development of HAART and there was very little evidence from resource-poor settings, home to 90% of people with HIV.

The table from the 2003 review is presented below without alteration (Table B-3) to illustrate the extent and also the limitations of knowledge at the time it was written. Review and comparison of symptom prevalence research, as done by Selwyn et al, has several methodological challenges. Tools used to record symptoms vary in the information recorded and the detail with which they are reported. For example, pain could be classified by the body region affected(35), the type of pain (ache, tingling, etc.)(36), the probable cause(37), or the intensity(38). This variation makes aggregation and comparison difficult. Even worse, many symptom reports do not give any methodological details, making it impossible to assess the reliability of the findings. The five papers summarised in Table B-3 give very little information on data collection methods beyond statements such as *'medical symptoms were assessed with a standard checklist'*(9), with no indication of the time period, the intensity, or how symptoms were selected or defined.

Table B-3: prevalence of symptoms in HIV, reproduced from Selwyn 2003(34)

	Moss(39) 1990 UK n=100	**Foley 1994 Canada n=100**	**LaRue(40) 1994 France n=314**	**Fantoni(41) 1997 Italy n=1128**	**Kelleher(9) 1997 UK n=118**
Symptom			% (rank)		
Fatigue	-	77 (2)	50 (2)	55 (1)	-
Weight loss	85 (1)[a]	91 (1)[b]	31 (6)	-	58 (1)
Pain	71 (2)	63 (3)	52 (1)	29 (4)	55 (2)
Anorexia	44 (3)	-	-	34 (2)	38 (3)
Anxiety	-	-	40 (3)	-	-
Incontinence	-	55 (4)	-	-	-
Insomnia	-	-	37 (4)	-	-
Hemiparesis/ataxia	-	-	-	-	23 (5)
Mouth sores	-	-	33 (5)	-	-
Cognitive dysfunction	32 (4)	43 (6)	-	-	19 (7)
Cough	30 (5)	34 (8)	27 (8)	32 (3)	19 (6)
Nausea/vomiting	24 (8)	35 (7)	28 (7)	22 (5)	17 (8)
Dyspnoea/ respiratory	17 (11)	48 (5)	22 (12)	19 (6)	15 (9)
Constipation	22 (10)	23 (12)	-	-	25 (4)
Fever/sweats	-	-	27 (9)	-	-
Pruritus/dry skin	27 (6)	24 (11)	23 (12)	17 (7)	-
Visual loss	-	25 (10)	-	12 (9)	-
Diarrhoea	23 (9)	-	24 (11)	11 (8)	14 (10)
Depression	26 (7)	32 (9)[c]	26 (10)	-	10 (12)
Headache	11 (12)	-	-	-	11 (11)

[a] includes fatigue [b] includes anorexia [c] includes anxiety

Research into the clinical symptoms of HIV sometimes attempts to exclude symptoms of other, presumed unrelated conditions and diseases(42). This approach is problematic. Firstly, a clear division between symptoms caused by HIV and those with external causes is difficult because HIV increases susceptibility to other infections and the pathophysiology of many symptoms is unclear. A symptom review of HIV-related nausea and vomiting in 1998 emphasised the need for research to better understand the aetiology of these common symptoms(43). Secondly, such an approach inevitably underestimates the symptom burden of individuals by measuring only a part of their total experience.

Table B-4 below updates the evidence for prevalence of physical symptoms in HIV. Symptoms which appear in five or more studies are sorted by average prevalence, from pain (61%) to breathlessness (32%). Four of these studies used the Memorial Symptom Assessment Scale-Short Form (MSAS-SF), and one used the SSC-HIVrev(44). Another study adapted an instrument (the HIV Symptom List) developed in the USA(35). No details of this process are given and the adapted instrument was apparently not validated in South Africa. The remaining studies developed new symptom assessment instruments, which were not validated. All ten studies were cross-sectional, giving no indication of how symptoms changed over time. All studies show that symptoms are extensive and varied.

Compared to the evidence in the 2003 review, these studies tend towards larger sample sizes, and the majority were conducted in Africa. Also, while some studies were aimed at measuring symptoms among those with advanced disease(45, 46), others recorded symptoms in HIV generally(47, 48). The study by Makoae et al, for example, used a cross-sectional, community based design, recruiting patients through home-based care programmes and outpatient clinics, which should have been more representative than a hospital-based sample because a wider proportion of patients would have access to the services and hence to the sampling frame(44). However, the cross-sectional survey design was applied without the use of a sampling frame or a systematic sampling method such as consecutive recruitment. As a result, the sample may be biased.

Table B-4: prevalence of physical symptoms in HIV (%)

	Vogl 1999 (46)	Mathews 2000 (48)	Selwyn 2003 (49)	Norval 2004 (45)	Makoae 2005 (44)	Shawn 2005 (35)	Harding 2006 (10)	Collins 2007 (47)	Uwimana 2007 (36)	Harding 2010 (50)
N	504	4042	84	103	743	64	347	731	250	778
Country	USA	USA	USA	South Africa	Botswana, SA[a], Lesotho,Swaziland	South Africa	UK	Tanzania	Rwanda	UK
Design	X-sect	X-sect survey	Chart review	X-sect	X-sect	X-sect survey	X-sect online survey	X-sect census	X-sect purposive sample	X-sect survey
Population	AIDS, ambulatory	National probability sample	AIDS, 73% inpatients	AIDS	Community based, HIV	Receiving palliative care	57% ART	Out-patients	Outpatients, inpatients, day centre	Outpatients
Time	Previous week	Previous 6 months	Previous week	Unclear	That day	Previous week	Previous week	Unclear	Unclear	Previous week
Measure	MSAS-SF	Novel	MSAS	Novel	SSC-HIVrev	HIV-SL	MSAS-SF	Novel	Novel	MSAS-SF
Pain (all)	76		48	98		89[b]	43	41[c]	47	53
Fatigue	85		41	43	56	65				68
Difficulty sleeping	74		21		32	55	59			62
Weakness				66	54		72	14	18	71
Weight change	43	37	16	81	57	74	28		4	
Skin problems	52	24	17	56	34	72	39	23		
Night sweats	56		12		41	44	40			
Cough	60		10	45	45	58	42	26	10	
Anorexia	51		26	71	44	33		9	8	
Diarrhoea	35	51	18	53	30	23	51	7	8	54
Fever		52	19		32	58			2	
Nausea/ vomiting	43	50	12	45	28	55	30	14	11	
Breathless	62		19		31	42		6		

[a] South Africa [b] localised pain only [c] excluding neuropathic pain

The prevalence of symptoms clearly depends on the period of time over which they are observed. Symptoms are more likely to occur within six months (as for the Mathews survey) than one week. On the other hand, long periods of time increase the probability that symptoms will be forgotten. The use of the MSAS in four studies here and the consistent time period of one week makes comparison more feasible. The Selwyn sample were receiving palliative care, and have fewer symptoms than the Vogl sample who were not.

The largest study used a probabilistic sampling method to randomly select a representative sample of people with HIV in the USA(48). In this case the weakness lay in the symptom assessment. A list of 14 symptoms was compiled, which was not based on piloting or previous research. As a result, symptoms such as pain and fatigue, which other studies found to be prevalent and bothersome, were not included. Despite its limitations, the evidence shows a very high prevalence of a wide variety of physical symptoms in HIV, in diverse settings and at different stages of disease.

Symptoms appear to be just as common with ART. In a large online UK survey using the MSAS-SF, gay men with HIV experienced a range of severe symptoms including pain, and those taking ART reported altered but equally burdensome symptoms(10), probably caused partly by side effects(51). In open-ended questions, participants said that they envisaged a future of shortened life and limited options, and many were “living without hope”(52). The most recently published study(50), based on data collected in 2006, reported on only the ten most common symptoms (of which three were psychological). Participants reported a mean of 17.9 symptoms and ART was not associated with symptom burden. In Zimbabwe, a cross-sectional study compared 96 women taking ART with 31 who were not yet eligible and 73 eligible but not taking it(53). Nurse-reported symptoms in the previous week were significantly fewer in the ART group (5.5 compared to 10.1 and 8.6, ANOVA $p<0.001$), but self-reported symptoms in the past year were only slightly lower (5.0, 5.8 and 6.0 respectively, $p=0.05$). Using the MOS-HIV, all groups had very similar physical health. These results suggest that health care workers observe a difference in symptom prevalence with ART which is not

reflected in patient experience. In the USA, Justice et al showed that health care workers detect only a third of patient-reported symptoms in HIV(54).

ART regimen change was associated with a particularly high symptom burden in the Women's Interagency HIV Study cohort in the USA(55). Due to the cross-sectional design it was not possible to establish whether participants had changed regimens because of a high symptom burden, or had experienced symptoms as a result of the new drug combination. Both could be contributing factors.

In 1999, a non-systematic review of fatigue in HIV derived a prevalence range from 20% to 60% from eleven published papers, but gave no information on the methodology or quality of these studies(56). The paper described fatigue as the '*most frequent and debilitating complaint of HIV positive people*'(56). A large cross-sectional survey in London with a good response rate found fatigue to be highly prevalent(65%), associated with psychological factors more than disease progression or use of ART(57). In South Africa, Voss et al discovered that the symptoms most closely correlated with fatigue were fever and depression, while a diagnosis of AIDS was also predictive of fatigue(58). The connection to depression supports the London findings, and the additional association with fever could be caused by environmental factors such as malaria.

A multi-centre study based in Colombia, Norway, Puerto Rico, Taiwan and the USA used the Revised Sign and Symptom Check-List for Persons With HIV Disease (SSC-HIVrev) to examine the prevalence of eight symptom clusters, including gastrointestinal (diarrhoea, gas, abdominal pain, nausea, vomiting), fatigue (weakness, muscle aches, painful joints, fatigue), and fever (chills, night sweats, fever)(59). Symptom cluster prevalence was consistently around 40% (plus or minus 3%) for those with no comorbid condition, and 50% (plus or minus 3%) for people with HIV plus depression, hypertension, hepatitis or diabetes.

B.1.iv Psychological problems in HIV disease

The issue of HIV-related psychological morbidity in resource-limited countries has been neglected(60), while receiving more attention in the developed world due to the well documented association of depression with ART non-adherence(61, 62). In 2007 The Lancet launched a series on global mental health(63), including one paper which reviewed the interaction between mental health and HIV, particularly in low- and middle-income countries(64). A 2006 systematic review of mental health and HIV in developing countries(60) identified, in Africa, five studies of QoL(65-69), three of prevalence(70-72), three of cognition in children, two of association with adherence(73, 74), and one tool validation(75). Two of these papers were different analyses of the same dataset(67, 71). More recently, other epidemiological studies of disease prevalence and risk factors have been published for mental health in Africa (76, 77).

Information on mental health conditions and symptoms in sub-Saharan Africa is summarised in Table B-5. The majority of evidence relates to depression, which is highly prevalent, and is often combined with anxiety. Two major limitations are the issue of tool validity, and a lack of longitudinal data. Only one validation study was identified(75) and several other studies imported an instrument from a different context without checking its properties. The first stage in the development of a tool to measure prevalence of psychological morbidity is to establish whether the cultural and linguistic context has a concept of mental illness that maps onto those conditions. An ethnographic study in Uganda found that people identified two HIV-related syndromes; one causing people to feel lonely, hopeless and uninterested, the other causing sadness, worthlessness and low energy, with both overlapping around sadness and excessive worry (69).

Table B-5: prevalence of mental health conditions with HIV in sub-Saharan Africa

Author, date	Population	Tool	Prevalence
Mfusi, 2000 (70)	N=30, pregnant, South Africa	Beck Depression Inventory (BDI)	23% severe anxiety 63% moderate/severe depression
Olley, 2003 (71)	N=149, outpatients, diagnosed within 1 year, South Africa	MINI	56% psychiatric disorder 35% depression 22% dysthymic disorder 15% PTSD
Sebit, 2003 (72)	N=194 Zimbabwe	Mini Mental	71% psychiatric disorder 57% depression
Hughes, 2004(68)	N=123, South Africa WHO stage 3/4, ART naive	EQ-5D	29% some anxiety/depression problems 4% severe anxiety/depression problems
Mast, 2004 (66)	N=239, women, with children <5, Uganda	MOS-HIV	22% 'felt depressed'
Jelsma, 2005(74)	N=117, South Africa	EQ-5D	Anxiety/ depression: 1 mth / 3 mth / 6 mth / 12 mth Some: 28% / 17% / 20% / 13% / 13% Severe: 3% / 1% / 1% / 4% / 1%
Kaharuza, 2006(78)	N=1017, Uganda Clinically eligible for ART and ART-naive	CESD	47% depressive symptoms (CESD >22) 19% 'distressed' (CESD 16-22)
Marwick, 2010 (76)	N=220, outpatients, Tanzania	Clinical Interview Schedule - Revised (CESD)	16% depression or anxiety/depression 5% other anxiety disorders
Kagee, 2010 (77)	N=85, outpatients, South Africa	BDI Hodgkin Symptom Checklist	38% moderate depression or above 53% elevated symptom distress

Only one longitudinal study was identified(74), and it had methodological limitations. The sample was not large (n=114), with attrition over time, and no statistical analysis was conducted, so the results could be due to chance. The paper found 28% of participants reported 'some problems' on the anxiety/depression question of the EQ-5D and 3% reported 'severe problems'. These results are very close to those found in a cross-sectional study which also used the EQ-5D(68).

Long-term observational cohort studies have linked depression to hastened disease progression and increased mortality risk(79). ART may be associated with

better mental health outcomes. In Zimbabwe, a cross-sectional study compared three groups of women; those taking ART, not yet eligible, and eligible but not taking it(53). Women on ART were significantly less likely to have depression according to a validated instrument, the Shona Symptom Questionnaire, and those on ART had better mental health with the MOS-HIV (56.0 compared to 44.1 for the non-eligible and 44.6 for the untreated). However, the direction of effect is not clear. People with depression may find it more difficult to maintain treatment, thus the effect of ART on mental health may be overestimated. A meta-analysis of ten studies of depression and ART adherence (80) found that people with depression symptoms were less likely to be classified as ART adherent (OR=0.45, 95% CI 0.31-0.66). Poor adherence could be the mechanism by which depressive symptoms are associated with mortality in people with HIV. It is also possible that people with depression may not be prescribed ART, which would also inflate the apparent benefits of ART on mental health in prevalence studies.

Alcoholism and addiction are risk factors for HIV infection in South Africa(81), and therefore are common comorbidities of HIV. There is evidence that alcohol use and abuse are also associated with ART non-adherence, although a meta-analysis was not conducted(80).

Mental health is affected biologically by HIV (and ART) and psychologically by the diagnosis of HIV(82), and these two effects can be confused. In the 1980s, neurocognitive symptoms such as forgetfulness, depression and personality change were observed in people who had been recently diagnosed with HIV and showed few physical symptoms, leading to the hypothesis that HIV often manifested first in the central nervous system(83). The Multicentre AIDS Cohort Study recruited and tested 4954 gay men of whom 36% were HIV positive, withholding their HIV test results until the end of the study(84). Self-reported physical symptoms and the lack of someone to talk to were associated with symptoms of depression in the cohort, but HIV status was not(85), showing that the early negative effects were more psychological than organic. It is likely that symptoms were also caused by the climate of fear, oppression, discrimination and multiple bereavement in which gay men were living at the time(86).

B.1.v Spiritual problems in HIV disease

Spirituality is often a central issue for those with life-limiting or chronic disease(87) and palliative care has always held spirituality to be a discrete and necessary domain of care. In South Africa and Uganda, palliative care patients (81% HIV positive) reported that feeling at peace and having a sense of meaning were more important to them than physical comfort or being active(88).

A systematic review of spirituality measurement in palliative care(89) identified and 34 individual tools and four tool 'families', consisting of a number of versions of the same tool. Of these, the four quality of life tool families (the WHOQOL-HIV, the POS, the MVQOLI and the McGill QoL Questionnaire) plus eight individual tools were used in HIV populations(Table B-6).

Table B-6: Spirituality tools used in HIV populations, from Selman et al 2011(89)

	Cross-culturally validated	Not cross-culturally validated
Quality of life instruments including spiritual element	WHOQOL-HIV(90, 91) MVQoLI(92, 93) McGill QoL Questionnaire(94)	QoL Ladder(95) FACIT-Pal(96)
Care outcome tools including spiritual element	POS	
Substantial measures of spirituality	Ironson-Woods(97)	Spiritual Activities Scale(98) Spirituality & Religion Survey(99)
Measures of spiritual distress	Beck Hopelessness Scale(100)	Coping Inventory(101) Measure of coping in HIV(102)

Studies of spirituality and HIV have been conducted primarily in the USA, and have found both positive and negative outcomes associated with spiritual beliefs and practices. Positive religious coping involves finding meaning in illness, reaching peace, and a concept referred to as transcendence. Spiritual struggle leads to feelings of guilt, anger, fear, and a sense of punishment(103). Negative religious coping is associated with anxiety and depression, and also with poor clinical

outcomes such as lower CD4 count(104). People with HIV may also experience ostracism from their religious community, although others derive great comfort and support from it(105).

A longitudinal study in the USA of over 400 people with HIV attempted to overcome the methodological weaknesses of previous studies by including a battery of spirituality tools(106). However, only two time points were used, limiting longitudinal analysis to a series of paired t-tests. Positive religious coping was associated with optimism and life satisfaction(106). These relationships may simply indicate the overlap between conceptions of coping and optimism inherent in the tool items(7).

B.1.vi Social problems in HIV disease

It has generally been thought that poverty was a risk factor for HIV infection in resource-poor countries, but more recent research has cast doubt on this claim(107). However, there is little doubt that poverty limits access to health care, hampers adherence, and is associated with greater symptom burden(108, 109). In the UK, a qualitative survey in 2004 concluded that the most salient needs for many people with HIV were food, transport, a safe place to live, addiction programmes, and mental health treatment(110). Social problems were more burdensome than physical symptoms. Physical and psychological symptoms can impair ability to work, which in resource-poor environments may limit the household's income and access to medication, transport and food(111).

De Waal and Whiteside proposed that HIV has altered the parameters of food production and famine risk in resource-poor countries, imposing both costs of care and loss of labour which reduce the resilience of rural households to external events such as low rainfall(112). Ill health reduces ability to work and therefore reduces income, as shown in a series of case studies which also demonstrated the effect on families of medical bills and the burden of caring for sick relatives and orphans(113). While the case studies lacked methodological rigour, the approach of quoting histories directly produced very credible results. It is an economic law

that as financial resources decrease, the proportion of total income spent on food increases(114), with the result that in extreme poverty a drop in income causes malnutrition.

A longitudinal survey of income and expenditure in 181 South African households found that the financial burden from death of a family member, both in cost of a funeral and the loss of income, posed the greatest challenge to the household(115). HIV is the primary cause of death in South Africa, and in 2004 caused 56% of deaths of working-age adults (aged 15-59), making HIV the major threat to families' economic survival(116).

Informal carers also have increased burdens as a result of HIV. In Namibia, carers of people with HIV were asked to keep diaries for an in-depth qualitative study(117). The paper argued that patients' increased dependency, morbidity from 'invisible' symptoms such as pain and fatigue, and loss of self-esteem caused great interpersonal stress within families. Social isolation as a result of inability to participate in reciprocal networks contributed to this stress for both patients and carers, and resulted in unsustainable damage to social bonds. This argument was given credibility by the use of quotes revealing fatigue and lack of resources on the part of carers.

B.1.vii Stigma and HIV

The consequences of being identified as HIV positive can include ostracism, verbal and physical abuse, and neglect(118). University students in South Africa reported in focus group discussions (FGDs) that fear of stigmatisation deterred them from testing(119). Farmer argues persuasively that HIV stigma is decontextualised, and should be seen as the visible manifestation of deep social inequality(120). In Haiti, stigmatisation was reduced when ART became available. The theory is that ART eliminates the equation of HIV with death, returns HIV to the nature of an ordinary disease, and makes testing acceptable.

The *Siyam'kela* project in South Africa attempted to understand stigma from internal and external perspectives. FGDs with patients and nurses in Lesotho, Malawi, South Africa, Swaziland and Tanzania explored the subject of stigma. Topics included the words and phrases used to refer to HIV(121), perceptions and experiences of status disclosure(122), experience of abuse and neglect(118), and coping strategies(123). Based on these findings, a conceptual model of stigma was developed(124), identifying three types of HIV stigma: received, internal and associated stigma. Received stigma is behaviour by others towards a person with HIV, internal stigma includes thoughts and behaviour by the person with HIV as a result of their own negative perceptions, and associated stigma is directed towards people who associate with those with HIV, such as health workers(124).

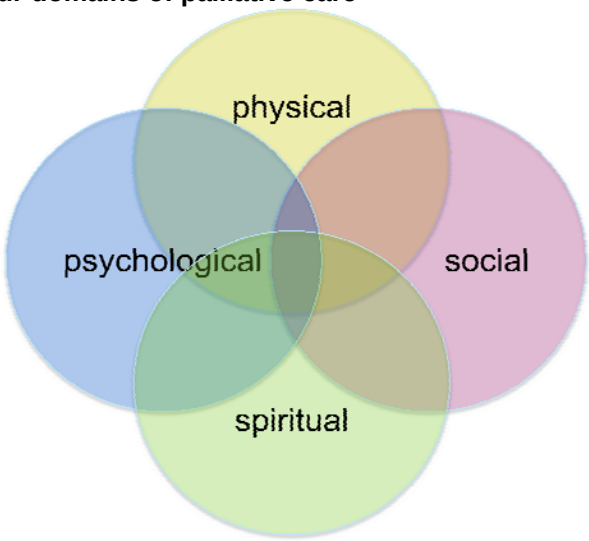
B.2 Palliative care

B.2.i Definition of palliative care

The defining features of palliative care are pain control and holistic, person-centred care(125). It is devoted to delivery of high-quality, person-centred, multi-professional care alongside curative treatment for people with life-limiting progressive illness and their families. Palliative care affirms life, accepts death and provides integrated, holistic support and symptom management(126). Palliative care is defined by the WHO as

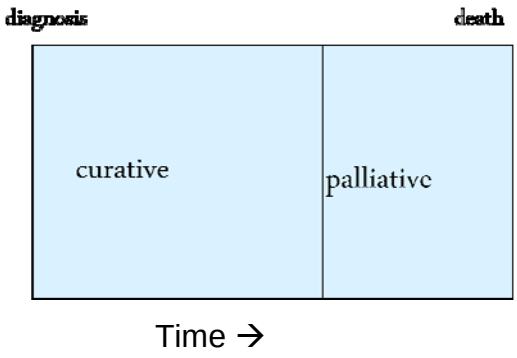
> *"an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual"* (11).

Figure B-1: The four domains of palliative care



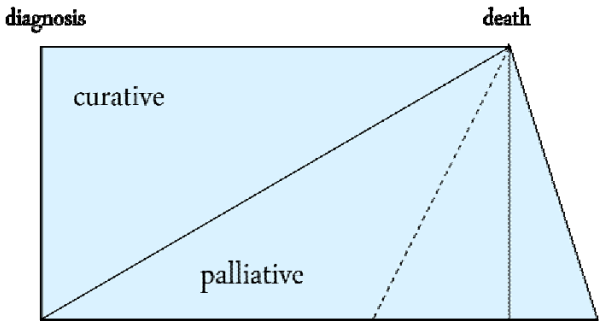
Palliative care originated in the care of the terminally ill at the end of life, particularly those dying from cancer(127). The original model of palliative care in the 1960s, represented in Figure B-2, conceived it as an option only when curative treatment had been abandoned.

Figure B-2: sequential model of palliative care



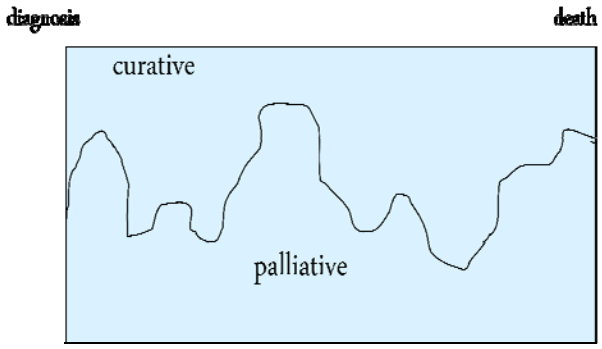
As it was realised that people have palliative care needs before curative treatment has ended, the model became one of gradual shift in priorities, as in Figure B-3 from the new palliative care definition of 2002(11):

Figure B-3: concurrent model of palliative care



However, in both these models, palliative care is not present at the time of diagnosis, even though the modern definition of palliative care is clear that it should be provided throughout the course of any life-limiting disease(8). The diagram below (Figure B-4) has been adopted by the American Thoracic Society to model individualised, integrated palliative care in conditions with an unpredictable course(128). In this model, palliative care begins immediately after diagnosis, and the balance between curative and palliative care can shift back and forth during the disease trajectory, according to the needs, burden, wishes and prognosis of the individual.

Figure B-4: personalised model of palliative care



B.2.ii Definition of HIV palliative care

Everyone diagnosed with HIV faces the problems associated with life-threatening illness. HIV palliative care begins at diagnosis, as made clear by the WHO and UNAIDS in their definitions of palliative care for HIV. The WHO defined HIV palliative care in 2006:

- "*Palliative care is a core component of comprehensive HIV/AIDS care.*
- *Access to palliative care should not be artificially restricted due to political or social constraints.*
- *All patients needing and wanting it should receive it, without exception.*
- *Palliative care should be provided in accordance with the needs of the patient and WHO standards of care.*
- *Treatment for illnesses and conditions should not be withheld at any stage of the disease (for example, tuberculosis (TB) treatment, antiretroviral treatment (ART) or substitution therapy for injecting drug users).*
- *Palliative care should be incorporated as appropriate at every stage of HIV disease, and not only when the patient is dying*"(129).

The WHO also establishes that

> *Ideally, palliative care and disease-specific treatment should be integrated throughout the course of chronic, life-limiting illness."* (129)

In addition, a particular commitment has been made to Africa in this regard:

> "*Palliative care should be an integral part of the comprehensive care and support for people living with HIV/AIDS (PLWHA) and cancer patients. It should be provided in the framework of a continuum of care from the time the incurable disease is diagnosed until the end of life*."(8)

UNAIDS published a technical update on palliative care in HIV:

> "*Palliative care is a philosophy of care which combines a range of therapies with the aim of achieving the best quality of life for patients (and their families) who are suffering from life-threatening and ultimately incurable illness. Central to this philosophy is the right that everyone has the right to be treated, and to die, with dignity, and that the relief of pain – physical , emotional spiritual and social is a human right and essential to this process*."(12)

In a palliative care toolkit for resource-limited settings, the importance of diagnosis was reiterated:

> "*Many people think that palliative care is just about looking after someone in the last few days of their life, but in fact it is about relieving suffering and improving quality of life right from the time when a person first finds out that they have an incurable illness.*"(130)

Finally, the Cape Town Declaration, written by African palliative care trainers at the founding of APCA, began "*palliative care is a right of every adult and child with a life-limiting disease*"(131). HIV remains incurable and life-limiting. All these policies and definitions agree that palliative care begins from the moment of diagnosis and alongside treatment, and that quality care is required at this time.

B.3 Palliative care at HIV diagnosis

The prime and sufficient reason to provide palliative care from diagnosis is that there is no justification for withholding palliative care from people who are known to have a progressive terminal illness. Palliative care at HIV diagnosis is a policy requirement, as shown in the previous section. A number of specific benefits of delivering palliative care at HIV diagnosis are discussed below.

B.3.i Patient-centred care

Palliative care is patient-centred by definition(132, 133). HIV care and research has been criticised as disease-centred(134), exemplified by the vertical approach to funding adopted by PEPFAR (135). In the literature, the time of diagnosis is often used as a proxy for seroconversion, a disease-oriented event which frequently goes unrecognised(136). Seroconversion, the development of antibodies specific to HIV, is the clinically detectable aspect of infection. Outcomes such as CD4 count and viral load are disease-centred, while mortality and QoL are patient-centred outcomes. From the patient's point of view HIV begins with diagnosis, not infection(137), and patient-centred care should address this by making diagnosis a key focus of research and care. Palliative care is also centred on the patient rather than the HCW, involving a multidisciplinary team.

Patient-centred care is also distinct from care provider-centred care. In South Africa, small pilot studies, followed by larger observational studies, have shown that patient empowerment results in excellent adherence(138). Patients are encouraged to take responsibility for their own health, including 'treatment literacy', training patients to understand their own drugs and to know the side effects and interactions of each. This programme was described as patient-centred. Mukherjee et al argue that breakdown in health systems is often blamed on the demand side (the patient), but that the problem is more likely to be on the supply side (the health care provider)(109).

B.3.ii Effectiveness

In order to deliver appropriate, effective palliative care at diagnosis it is essential to understand the problems which occur at this time. The clinical care and public health approaches to HIV can appear to be in conflict. Maher and Harries proposed looking at HIV through a ‘quality lens’ to bridge the two(139). Quality clinical care is integral to palliative care(11).

It would be difficult to argue for palliative care in HIV without evidence that palliative care improved outcomes for people with HIV. A systematic review of the effectiveness of HIV palliative care was carried out in 2005(140). The search strategy found 17 service evaluations of which one was graded ‘strong evidence’, two ‘fairly strong evidence’, seven ‘weak evidence’, and six were qualitative. The best-quality study, a randomised controlled trial(RCT) of multiprofessional home care over standard care, showed improved wellbeing and survival in the intervention group but this did not reach statistical significance. The variety of systems by which palliative care can be implemented, coupled with the wide range of evaluation methods, made meta-analysis unsuitable. Services included home care, inpatient hospice care and community support teams, usually in Europe and North America, with three in sub-Saharan Africa. The most consistent evidence showed high patient satisfaction and lowered symptom prevalence.

B.3.iii Retention, ART adherence, and mortality

Morbidity and mortality risks are much higher for patients who begin ART with a very low CD4 count(141), and the most common reason for this is late presentation for care. Late HIV diagnosis is often not distinguished from late entry into care(142). To avoid late initiation of ART, the connection between the patient and the health service should be maintained.

Figure B-5: representation of patient trajectory

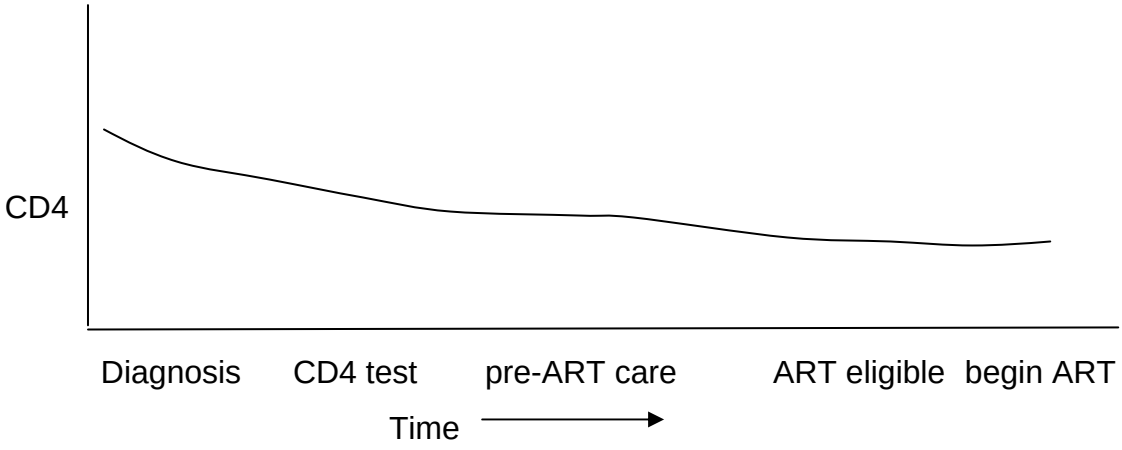


Figure B-5 represents the health care services of a patient from HIV diagnosis to the initiation of ART, assuming that the patient is not eligible for ART at diagnosis. The patient completes a CD4 test and returns for the result, and is admitted into pre-ART care with regular tests to check for disease progression. When CD4 count and clinical criteria indicate that the patient is eligible, then ART treatment is initiated.

In reality, the majority of patients are not retained in care continuously for this time. Rosen and Fox conducted systematic reviews of LTFU from HIV care in Africa both before (143) and after (144)ART initiation.

Pre-ART care was grouped into three stages; from positive test to CD4 result (stage 1), pre-ART care until eligibility (Stage 2) and, for ART eligible patients, pre-treatment to initiation (Stage 3). Of all patients tested, a median of 59% (range 35-88%) received a CD4 count result or a clinical staging. From this point, 46% (31-95%) of ineligible patients were retained in pre-ART care until they became eligible. Of those identified as eligible, 68% (14-84%) completed ART initiation.

The reviewers identified a lack of standardised indicators and outcomes for retention in care, and few papers could be idnetified, given the wealth of experience in the area and the critical importance of retention in care for patient wellbeing. Severeal papers used data censoring as an endpoint, i.e. determining what proportion of all registered patients were alive and still in care at the time of

the sruvey. This simplistic method does not make the best use of the data. A patient-relevant endpoint such as ART initiation of a fixed period of time would be a better way of estimating LTFU.

Retention in ART programmes is more closely and systematicelly monitored, which enabled Fox and Rosen to use a random effects meta-analysis of the 226,307 patients from 33 identified sources. Using this approach, retention in care was 86% six months after ART initiation, 80% at twelve months, and 77% at 24 months.

Table B-7 summarises the evidence for LTFU of pre-ART patients by CD4 count, showing that a higher CD4 count is predictive of even worse retention. For example in Johannesburg the great majority(85%) of patients with CD4 greater than 200, and half of those with lower CD4, do not return for their CD4 test result within six months after their HIV diagnosis(145). To some extent this shows a sensible prioritisation of those in greatest need but it also reveals that the high LTFU is more likely to be caused by structural differences in care than patient inability to remain. Tayler-Smith et al explained that monitoring and follow-up of pre-ART patients in Malawi was carried out by the general outpatient department rather than the HIV clinic. After six months, retention was 90% for patients on ART versus 16% for pre-ART. Clinic resources were focused on retaining patients on ART, and less physically sick patients were not actively encouraged to return for care.

This much lower LTFU of ART patients shows that retention is possible. ART patients gained access to the HIV clinic facilities, including trained counsellors, community-level peer to peer counselling, and a much lower ratio of patients to clinicians. This care had an immediate effect on retention (and thus reduced morbidity and mortality) from the first point of contact. Similarly, the very simple intervention of free cotrimoxazole (a broad-spectrum daily antibiotic) was associated with a significant ($p<0.001$) improvement in pre-ART patient retention in Kenya(146). These findings show that good care can reduce LTFU. Reported obstacles to retention include pain, sickness, hunger and hopelessness(147). Palliative care can help to ameliorate these problems. Patient-centred assessment and management of common problems at diagnosis may be able to improve retention.

After patient retention, ART adherence is the second major concern of HIV programmes(148). Patient-centred outcomes such as quality of life are not part of routine follow-up of ART patients(149), even though adherence is known to be affected by perceived quality of care, mental health(150), and social support(151, 152). A third of HIV patients in South Africa are eligible for ART at diagnosis using the criteria of CD4<200(153), and the new WHO guideline of initiation at 350 cell/ml can only increase the number of patients who require immediate ART. Patient-centred palliative care at diagnosis would identify and manage problems that limit patients' ability to adhere to treatment.

The reasons why people fail to maintain treatment have been explored through qualitative research, finding that the main impediments to ART adherence are lack of money, problems obtaining transport, and shortage of food(154). Nutrition and poverty reduction are elements of holistic palliative care. Symptom burden is associated with reduced ART adherence(155) and with a greater probability of switching ART regimens in settings where this is a possibility(55). A qualitative study of barriers to adherence in Tanzania analysed the results with a socio-ecological framework, identifying structural, programmatic and community barriers(147). However, in the interview quotes, participants spoke of hunger, fatigue, hopelessness, confusion, vomiting and pain. Symptom management could improve adherence and therefore life expectancy.

B.3.iv Prevention

As quoted above, palliative care incorporates the prevention, as well as the relief, of suffering(11). Meeting care needs promptly and appropriately might prevent other health problems later. The initiation of palliative care immediately after diagnosis would allow problems to be identified and managed quickly. The result of pre-ART LTFU is that patients either die or return with advanced disease, as 'late presenters'. In Malawi, patient tracing revealed that of 694 pre-ART patients lost to follow-up, 49% had died, and 54% of the 451 ART patients had died(156). Median time from default to death was respectively 47 and 52 days. Some of these deaths could have been prevented with appropriate care and the prevention of default.

Table B-7: retention at HIV diagnosis, CD4 testing and pre-ART care by CD4 count and care

Author, date, setting	Intervention	n	CD4	Retention (%)	
				3 months	12 months
Larson 2010 (145), urban South Africa, awaiting first CD4 result		161	>200	15	
		191	0-200	51	
Bassett 2010(157), urban South Africa, newly diagnosed, ART-naive		358	<200		39
Larson 2010 (158), urban South Africa, enrolled in pre-ART care		228	>350		26
		128	251-350		41
Lessells 2011(159), South Africa, time since first CD4 count		1340	>500		35 (95% CI 32-37)
		1278	351-500		43 (95% CI 41-46)
		1605	201-350		52 (95% CI 49-54)
Kohler 2011(146) Kenya, pre-ART	Free cotrimoxazole	414			84
	No free cotrimoxazole	610			63

B.4 The history of HIV and palliative care

B.4.i 1960s: Origins of palliative care

Palliative care had its nineteenth-century beginnings in small homes for the dying, where nursing, companionship and spiritual support were given to the terminally ill whom hospitals would not accept(160, 161). Modern palliative care came into being through the efforts of Cicely Saunders. Practising firstly as a nurse, then a social worker and later as a doctor, she introduced effective pain and symptom control(162), and in 1967 opened the world's first modern hospice. She later recalled that to the existing model were added three key ingredients: listening to and systematic recording of patients' experiences(163); an emphasis on pain control as a preventive rather than responsive measure; and the concept of 'total pain', the inseparability of physical and mental suffering(164). While palliative care has been redefined over the years its core values remain preventive pain control and interdisciplinary, patient-centred holistic care.

Early work by Hinton in the 1960s had explored the experience of dying in general, from any disease(165), but palliative care was initially focused on end-of-life cancer care, because Saunders felt that these patients were the most neglected by medicine(164). The typical hospice patient received symptom relief, pain control and psychosocial care, usually in the few weeks of rapid physical deterioration from a diagnosis of terminal cancer to the end of life(163). Home care was developed in the 1970s and greatly expanded following the publication of the Wilkes Report in 1980(166), which recommended integration between the primary sector, hospitals and the hospice movement. The first palliative care hospital support team was formed at St Thomas' in 1978, transferring the principles of hospice care to a new setting.

By the beginning of the 1980s palliative care was established in the UK, in numerous semi-independent hospices as well as specialist hospital teams(164). By this time, hospices existed in Europe, Africa and North America, and the definition

of palliative care had expanded to other progressive diseases besides cancer. In the USA, hospice care was seen as counter-cultural, delivered more by nurses than by doctors. Congress added hospice benefit to the Medicare scheme for over-65s in 1982. Palliative care also developed in Canada (where the phrase was coined), pioneered by Balfour Mount(167).

B.4.ii 1980s: Development of AIDS palliative care

The hospice movement had found a respected place in the care of people with cancer(168). Expansion into other diseases was always intended, but there was no immediate haste to do so while the nascent hospice movement was still developing its skills and expertise. The recognition of AIDS in 1981 forced the issue. The hospice movement was faced with a new, universally terminal condition with severe symptom burden and a life expectancy of nine months from diagnosis(169). Many of the first HIV care providers were palliative care specialists(170-172).

There was considerable debate around whether people with AIDS should be admitted to the existing, predominantly cancer-based hospices or whether they would be better cared for in HIV-specific units(168, 173). Independent or semi-autonomous hospices and palliative care teams made the decision individually. In 1987, the hospice movement told a parliamentary committee it was unable to manage AIDS care(174), although Princess Alice Hospice had already been admitting HIV patients for two years. The movement was diverse and accommodated different perspectives. The same year, the American Journal of Hospice and Palliative Care hosted a debate on the suitability of hospice for AIDS patients. While aware that many hospices were already accepting people with HIV(175), the editorial pointed out that the decision should not be taken lightly and that if a hospice was to take AIDS patients it must be able to provide effective care(176). The Ritter Scheuer Hospice described the process by which it decided to accept HIV positive intravenous drug users and the training program it put in place for staff(177).

Arguments in favour of accepting HIV patients into the hospice system were based on

- The rising number of people with HIV and the urgency of the need(175)
- The history and ethos of palliative care, whose principles were always meant to apply to non-cancer conditions(168)
- The skills developed in caring of for the dying, making HIV care a logical extension of the procedures already in place(176)
- The scarcity of supportive care. HIV fell between three traditionally under-resourced specialities – infectious disease, genito-urinary medicine, and palliative care – the first two of which had no experience of terminal care. Furthermore, hospice staff thought that stigma and fear caused neglect in many health care settings and homes(178). Nurses were fearful, homophobic, ill-informed and unwilling to care for people with AIDS(179).

However, there were strong arguments against taking people with HIV into hospices which predominantly served cancer patients. In the 1980s, the fledgling hospice movement had yet to be universally recognised as a valid health care provider. It was argued that the movement should focus its resources on the area of end-stage cancer, in which it had developed skills, confidence and expertise. Rapid expansion could result in diminished quality of services which would damage the reputation of palliative care as a whole(168). Furthermore, stigmatisation of people with HIV was rife. A hospice which accepted patients with AIDS could lose the goodwill and financial support of the community. In the USA, local residents near to hospices campaigned to prevent them accepting HIV patients, and were often successful(180).

At Ritter Scheuer Hospice in New York, unexpected problems in the care of people with HIV (around half of whom were infected through injection drug use) included(177)

- homelessness(181) or a home that lacked basic sanitary requirements for care, requiring inpatient care until death
- continuing narcotic abuse by family members, necessitating limit-setting by staff which was contrary to the ethos of palliative care
- increased psychological stress on staff due to the young age of patients
- secrecy, which frustrated attempts to support bereaved families who were not aware of the cause of death.

- discrimination from funeral directors and other service providers who refused to accept people with HIV

Hospice staff were concerned that they lacked the skills to manage HIV effectively (168, 178). Physically, people with AIDS experienced hitherto rare problems including cytomegalovirus, Kaposi's sarcoma, and HIV encephalopathy(9), as well as challenging conditions such as cognitive dysfunction, ataxia, blindness and chronic diarrhoea(182, 183). Rather than the predictable decline characteristic of cancer, HIV was subject to sudden fluctuations, and the end of life was difficult to identify(39). In the last six weeks of life, patients suffered from dyspnoea, cough, weakness, diarrhoea, weight loss, anxiety and depression(184). Treatment regimens were frequently complex and burdensome, including long-term intravenous drugs(39).

Psychosocial and spiritual problems were also challenging. HIV patients were younger than typical hospice patients, with the reputation of being vocal and 'difficult' (185). Hospice staff reported(186) that people dying of AIDS were typically younger than their usual patients, with more restricted financial resources, less social support, and very different spiritual needs(187). Mildmay staff in the UK found that their patients often needed practical support such as help with welfare, housing and disability benefits, will writing, visas, and funeral planning(187). There were social problems for patients with distant or estranged families, and with same-sex partners who had very few legal rights or recognition. Psychological and counselling issues included guilt and anger, self-blame, the consequence of changed body image(39), fear of dementia and fear of dying young.

Feelings ran high. At the first Annual American Conference on Hospice Care in 1985, Kubler-Ross gave the keynote speech, in which she said "*A hospice that doesn't accept AIDS patients should not be called a hospice*"(178). Kubler-Ross believed hospices' reservations were primarily based on prejudice, fear and lack of compassion(173). When she called HIV "*the ultimate challenge*" to palliative care(188), she referred to the challenge of offering love and care to people with HIV, not the technical management of symptoms. Saunders later regretted that the palliative care movement had been slow to accept the challenge of caring for people with AIDS(163).

More hospices began to accept people with HIV(189), but specialist centres were also developed(187). Coming Home Hospice in San Francisco set aside ten of its 15 beds for AIDS patients when it opened in 1987(39). The following year saw the opening of Casey House Hospice in Toronto (186). In London, Mildmay deliberately based its programme of interdisciplinary, patient-centred care on the terminal care at St Christopher's(187). Specialist HIV community support teams and day centres(7) were developed following the model of palliative care for cancer(184). People with HIV or AIDS were referred for specialist care with symptom control, anxiety or patient support problems(172). Anecdotal evidence suggested that in the UK people with HIV preferred to be treated at a designated HIV centre(183), believing their needs would be best met there.

In contexts that did not explicitly refer to palliative care, AIDS nursing emphasised holistic issues such as home based care, family support, pain management, anxiety control, spiritual care and bereavement issues(190). User-led services(191) also laid great importance on interdisciplinary, integrated and continuous care(192).

B.4.iii 1990s: Divergence of palliative care and HIV care

HIV challenged the definitions of palliative care(193), and its boundary with curative care(194). Interviews with health care providers and patients in London revealed the problems of co-management between HIV specialists and palliative care teams(195). Each professional group saw itself as best placed to coordinate services and prevent duplication.

In 1995 the Journal of Palliative Care devoted a special issue to HIV, revealing some of the emerging tensions between palliative care and HIV care. Grothe identified three challenges to palliative care for people with HIV: the disease, the person, and the context(196). Firstly, the unpredictable trajectory of HIV, compared with the more predictable decline typical of cancer, led to difficult decision-making and complex care regimes. Staff struggled to balance the provision of aggressive

treatment with palliative care in a blend that satisfied patient autonomy and comfort. From Foley et al (186):

> "*In the 1980s, treatments were complex enough. Now in the 1990s, PHAs may live with multiple infections, increased longevity, multiple cancers … and a higher burden of suffering than ever before. This raises questions such as: what is the purpose of our care? Is multiple drug therapy truly palliative?"* (p20)

Aggressive treatment could be necessary even in late stages of illness to prevent or cure infections. Intravenous therapy to combat viral retinitis, for example, might continue until death (197). This simultaneous provision of aggressive and palliative treatment was problematic for some. Kuhl asked (198)

> "[S]*ome of the infections experienced by a person with AIDS are reversible while the disease itself and the depletion of CD4 cells continues. When does palliative care begin? … Does palliative care mean that all symptoms will be treated only symptomatically when symptoms are due to a reversible infection?"(*p27)

His solution was that the palliative care team must combine both components, active treatment and palliative care, as appropriate. This approach endures as a principle of palliative care.

Secondly, people presenting with HIV had different needs from the typical hospice patient. In the USA and Canada at this time, most people with HIV were gay men, injection drug users or people from ethnic minorities (black or aboriginal Canadian), cultures with which most hospice workers had very little experience. Robb asked

> "*how can we provide hospice care for persons for whom AIDS is just one problem in a long list of overwhelming, life-threatening concerns?*" (199)

This comment referred to injection drug users who might also contend with homelessness, mental health problems, lack of family and social support, addiction and poverty (200). People with HIV might have a history of activism and challenging medical authority to obtain treatment(194), and they sometimes experienced grief and emotional exhaustion from over a decade of bereavements(169).

Lastly, the context of care provision was not always suitable for HIV. Advocacy groups lobbied for a separate HIV service, and generalist palliative care staff were unsure of their ability to manage HIV patients(197). American hospices were faced with financial issues; hospice care was funded for the last six months of life and was expected to exclude active treatment, but HIV palliative care might require expensive medication and the end of life was unpredictable.

There was concern that if HIV palliative care was delivered at all stages of illness and should include aggressive therapy when appropriate, then it would take on an unmanageable responsibility for all care, rather than establishing core generalist palliative care skills across the various HIV care settings. This dilemma was resolved by the separation of HIV care from palliative care, as the advent of HAART made HIV potentially a chronic (though still incurable and life-limiting) condition, rather than a predictably terminal disease. Mortality from AIDS dropped rapidly after 1995 in developed countries where HAART was available(201). AIDS hospices adapted to the changed disease; Mildmay specialised in HIV brain infection rehabilitation, the Sydney Sacred Heart Hospice reverted to generic palliative care, and the London Lighthouse closed its residential unit (202). In 1999 the closure of Chicago House (one of the last HIV-only hospices in the USA) was hailed in the media as a triumph for protease inhibitors, although the manager of Coming Home Hospice in San Francisco warned that the number of HIV patients had begun to rise again(203).

B.4.iv 2000s: Rollout of ART and relationship with palliative care

By the end of 2007 around three million people worldwide were receiving ART, and a further six million were estimated to be in need of it(204). In the new era of ART, HIV care lost contact with its palliative care origins(205). Selwyn, a palliative care specialist who described himself as having become an HIV physician by accident, warned that “*we run the risk of forgetting what we learned about healing, from a disease that we could not cure*”(206). He was concerned about the relationship between curative and palliative care (207), two approaches which should have

been complementary but were often viewed as exclusive alternatives. This false dichotomy, common to many diseases, was particularly apparent in HIV because aggressive treatment for infections could be required until the end of life, and because HIV care had begun in the spirit of palliative care. The separation was widened by the common view which equated palliative care with terminal care and death, rather than seeing it an approach to improve patients' QoL from diagnosis onwards. While palliative care was considered a last resort, there was a reluctance to do anything that suggested 'giving up'(39), particularly as most people who died of AIDS were young(208).

B.4.v 2010s: HIV palliative care evolves

Palliative care was redefined to return to its original purpose, delivering care based on need rather than on diagnosis (i.e. cancer) or prognosis(209). Services were developed for patients with heart failure, COPD and other non-cancer conditions(210), and care protocols and policy for the management of incurable progressive non-cancer diseases began to stipulate the inclusion of palliative care. HIV was included likewise, but palliative care was now one of a number of services, not a core provider of HIV care as it had been in the past.

Despite high prevalence of pain and symptoms throughout the trajectory of HIV(34), and the high mortality rates(15, 24), less than one percent of the papers presented at the last four biennial International AIDS Society conferences related to palliative care(211-214). The journal AIDS has published only five articles on palliative care in its 20-year history(39, 103, 212, 215, 216), even though the first of these opened with the sentence (equally true today):

> "*it could be said that all care in AIDS is necessarily palliative, since no specific cure has yet been found*." (39)

While expanding into heart failure and other non-malignant diseases, the palliative care movement aimed to provide palliative care to everyone in the world who needed it, by adopting a public health approach(217). In 2007 the method of integrating palliative care into existing healthcare services which had been pioneered in cancer(218) was developed further into a Public Health Model

applicable to all life-limiting disease(217). The WHO also produced guidelines for community based HIV palliative care as part of the series on Integrated Management of Adult/Adolescent Illnesses (IMAI)(126), and UNAIDS published a palliative care manual(12).

In 2000, a conference on ‘palliative care in the age of HIV/AIDS’ brought together the palliative care experience of the UK and the HIV experience of the USA (219, 220). More than the age of HIV, the conference was set in the era of ART(221). Palliative care had gone from being a central provider of HIV care to having a minor role, generally in terminal stages. Now, redefined, its appropriateness depended on need rather than diagnosis or prognosis. The increasing life expectancy of people with HIV also made them more vulnerable to comorbidities such as malignancies and liver disease(222). However, mortality for people with HIV remained higher than average even with the best health care(223).

Selwyn summarised the evolution of HIV care:

> “*For a brief period in the early years of the AIDS epidemic in the developed world, AIDS care and palliative care clinicians worked closely together, or were even the same people, in many settings where the only care for AIDS was palliative and end-of-life care. Thankfully, with the advent of highly active antiretroviral therapy (HAART) and the expansion of other therapeutic options in the past two decades, the field of HIV has developed its own expertise, just as palliative care has further established itself as a clinical and academic discipline. However, as the disease has evolved, we have seen the emergence of a false dichotomy between curative and palliative care, which does not serve the patient well and does not fit the evolving nature of the disease*”(224)

Selwyn and Rivard called for “*the distance which has developed between HIV and palliative care to be bridged*”(34) in a 2003 review of the literature, but the evidence they cited for pain and symptom experience dated from the pre-ART era(9, 39-41). The paucity of research investigating the effectiveness of palliative care post-ART, or even the prevalence of multidimensional symptoms and problems, demonstrated the growing gulf between the disciplines of HIV and palliative care.

B.4.vi HIV palliative care development in Africa

Early African HIV care was relatively multidimensional and community-based, with services including counselling and family support, but limited control of pain and symptoms(225). In the UK, holistic HIV care, modelled on Saunders' palliative care but evolving independently, had become the accepted way to care for people with AIDS. That method was transferred to Africa, as from 1989 onwards UK Mildmay staff conducted study tours and training partnerships in Africa, opening the Uganda Mildmay Centre in 1998.

Meanwhile, specialist palliative care grew alongside HIV care in Africa, expanding its services from cancer to HIV as HIV became the primary cause of adult death. Island Hospice in Zimbabwe took its first AIDS patient in 1986, and South Africa soon followed, followed by Kenya in 1990. The following year, Saunders was the guest editor of a special palliative care issue of *Contact*, the magazine of the Christian Medical Commission. Dr Anne Merriman contributed an article describing her experiences at Nairobi Hospice(226), which led to the founding of Hospice Africa Uganda, a 'model hospice' for resource-poor countries(227), delivering home-based care for people with terminal cancer(225) and, very soon, for HIV. In Uganda, palliative care spread using the WHO Public Health Strategy(217) to integrate palliative care into the healthcare system. Medical students have received palliative care training since 1994. It has been suggested that the successful expansion of palliative care in Uganda was directly related to its connection with the HIV epidemic(228).

Facilities were scattered and unconnected. In 2001, the Diana, Princess of Wales Memorial Fund launched a Palliative Care Initiative to champion and support the growth of palliative care in sub-Saharan Africa, particularly in HIV(131). A review of African palliative care in 2005(229) identified four countries where palliative care was approaching integration with mainstream health services, eleven with localised provision of hospices, eleven where capacity building was underway and 21 without palliative care activity(230). The founding of the African Palliative Care Association(APCA) in 2002(131) represented a major step forward for the development of African palliative care. Its role was to "*nurture communication,*

coordination, collaboration and advocacy", linking the small and disparate palliative care services into health care systems and with each other.

In Africa, palliative care developed alongside the rollout of ART, and as a result has been more integrated and less restricted to the terminal phase. A survey in 2003(231) found that 91% of responding HIV end-of-life services were integrated with prevention programmes, 77% addressed the effects of poverty on care, and 65% accepted patients from the point of HIV diagnosis, in line with WHO policy. The majority of programmes conducted education, training and advocacy as well as care. Integration of palliative care with HIV care allowed HIV care services to refer their patients for specialist palliative care without needing to meet rigorous opioid prescription standards themselves(232). A paediatric hospice in South Africa used specialist palliative care and symptom management to initiate children onto ART(233). Coverage expanded through referral networks and training, facilitated by the production of practical guidelines such as the Palliative Care Toolkit for resource-limited settings(130). The definition of palliative care has expanded to include provision of food, income generation programmes(231), orphan care, and similar social interventions(234), underpinned by the concept of patient-centred total care.

The President's Emergency Plan for AIDS Relief(PEPFAR), the US$15 billion fund developed by George Bush, took guidance from HIV physicians from the pre-ART years of the pandemic, and gave palliative care equal standing with prevention and treatment as a third essential and complementary goal. A special issue of the Journal of Pain and Symptom Management focused on social justice(133, 224, 235, 236), emphasising that palliative care must always be accompanied by ART.

The same lessons about the importance of multidimensional care were being learned by care providers outside the palliative care movement. In an observational study, a package including home-based symptom management, support for family carers, referral of patients with risk signs, continuous adherence counselling and defaulter tracing alongside ART resulted in 97% survival (of all those registered in the previous 21 months) compared to 85% with ART alone(237). Loss to follow-up (LTFU) became a key area of importance to HIV care(158), and the programmes with the lowest LTFU were those which delivered decentralised care at community

level(238) through primary health clinics(239). The DART cluster-randomised controlled trial found that home-based ART was just as effective as a clinic-based programme in terms of mortality and virologic failure (although, notably, QoL and symptom burden were not measured)(240). These programmes were successful because they delivered holistic, quality care, including social support, counselling and medical treatment. The same principles were observed in Cameroon where decentralisation of ART services resulted in better psychological outcomes and quality of life(241).

B.4.vii Conclusions

At the beginning of the HIV pandemic, palliative care was still widely understood as care for those with terminal illness, and as so interpreted it was central to HIV care. Treatment innovations changed the nature of HIV disease, and with improved life expectancy it was only appropriate that terminal care should assume less significance. HIV care diverged from palliative care while maintaining the holistic principles of the hospice movement at its heart. HIV clinicians and researchers, and people with HIV, lost contact with palliative care specialists and overlooked the evolution of palliative care to its more modern definition, now encompassing all those with a progressive life-limiting condition. As a result, contemporary HIV care aims to be holistic but is no longer palliative. HIV care specialists do not recognise a need for palliative care other than at the end of life. People with HIV do not have access to palliative care before the terminal phase, although there is evidence they would benefit from it in terms of improved outcomes.

B.5 Challenges to HIV African palliative care research

Surveys of African palliative care (232) illustrated the processes taking place and revealed a wealth of experience for both HIV and cancer, but evidence of effectiveness was undeveloped(232). Two papers in 2008 identified challenges to African palliative care research(242, 243). Many of these challenges were common to all health research, while palliative care also faced concerns from its connection with opioids, and was not seen as a priority in HIV research(244).

B.5.i Logistical problems

Logistical problems include limited and dysfunctional infrastructure, limited research funding, shortage of trained local researchers and lack of a career path allowing them to progress(243). Palliative care associations from around the world signed the Declaration of Venice in 2006, affirming the importance of palliative care research in developing countries to ensure maximum benefit for patients(245). High quality research producing robust evidence was seen as essential for the changes in policy and practice required to develop palliative care, especially in a situation of limited resources and competing demands(242).

Only one study has been identified which attempted to measure the proportion of people with HIV who would benefit from palliative care(47). ‘Needs appropriate for palliative care’ were defined as an unresolved symptom, pain, or a complex psychosocial or spiritual need, as recorded by a HCW. Appropriate needs were identified in 52% of 731 patients who visited the hospital. The severity of problems and the requirement for generalist versus specialist palliative care could not be established. Furthermore, need assessment was limited by the use of a closed checklist to record symptoms. A paper in 2002 calculated that if 6% of the population of Uganda was HIV positive and a sixth of these had AIDS, while 0.1% had cancer (half of whom also had HIV), then at any one time 240,000 people in Uganda were in pain(246). The estimates of disease and pain prevalence were highly unreliable, and the calculation did not allow for the fact that people with HIV experience pain prior to AIDS. This limited information hampers service planning. It is notable that the figure of 240,000 was made up of 220,000 people with AIDS and

a tenth as many with cancer, demonstrating the primacy of HIV/AIDS in African palliative care.

B.5.ii Methodological problems

Methodological problems included inadequate mechanisms for ethical clearance, sources of bias such as the diversity of languages, power imbalance between health workers and patients, and lack of sampling frames to allow probabilistic sampling(242). Studies reported process data only, such as the evaluation of an inpatient palliative care unit which reported the average length of stay but no patient outcomes(247).

The absence of a validated outcome measure was a major problem, identified as a need by African researchers(231). The lack of appropriate, validated measures hampered the development of a rigorous evidence base (242). Outcome measures used in palliative care settings in Africa include:

- The MOS-HIV – a health related QoL instrument developed in the USA(248) and adapted and validated in Uganda(249).
- A symptom questionnaire for people with HIV, not described or validated(45)
- The HIV-SL and HIV-SP - an HIV symptom list and symptom profile, piloted in the USA, adapted in South Africa but not validated(35)
- A questionnaire to identify needs of people with terminal illness, developed in Uganda(250) and adapted in Rwanda(36)
- The MVQoLI(93), developed in the USA for use in end of life care

These instruments were inadequate for palliative care research, either because they were one-dimensional, too long, unvalidated, or because insufficient evidence had been provided to judge their worth. Tools were often developed at one service and not adequately validated or shared for general use. The MVQoLI, a palliative care instrument, was designed for clinical use and of limited value as a research instrument, as well as being relevant only to those with advanced illness(92).

Symptom questionnaires such as the MSAS-SF, while very useful, have limitations in that they do not include multidimensional problems and usually consist of a

closed list of symptoms. Closed lists are useful for generalisation and comparison, but they limit data to the expectations of the researcher. Thus, important areas such as psychological or spiritual problems may be absent. Some QoL instruments have been developed for a Western context and then used in Africa without validation.

B.5.iii Confusion around QoL

A more general problem with QoL instrument design also emerged in the quest for a suitable outcome measure. Bowden and Fox-Rushby described how adaptation of QoL instruments for a new cultural context can suffer from '*misguided pre-occupation with scales rather than the concepts being scaled and too much reliance on unsubstantiated claims of conceptual equivalence*'(251). Gatter describes the methodological difficulties with much of the research on coping and QoL, particularly when subjective concepts of wellbeing or social inclusion are reduced to multi-item scales for covariance analysis(7). Firstly, correlations are misinterpreted as causative relationships, while the correlations themselves may be generated by the overlapping cultural meanings of concepts (such as self-esteem and social support), amounting to tautology. Secondly, in being quantified, concepts also be reified, decontextualised, stripped of meaning, and unrepresentative of the social environment they were meant to express. A way to avoid these problems may be to measure patient experience more directly, rather than creating multi-dimensional summary scores.

B.5.iv Development of an outcome measure: the APCA African POS

The APCA African POS was created to meet African palliative care providers' expressed need(231) for a multidimensional palliative care scale(252). It is based on the original POS, which was developed to address the multidimensional problems of patients with incurable progressive disease and subsequently adapted around the world (253, 254). The POS itself was developed form the Symptiom

Treatment Assessment Schedule (STAS), which was the main tool for evaluation of palliative care needs in the 1990s and was used at the first HIV palliative care service in the UK.

To create the African POS, an expert panel representing four African countries reviewed the WHO definition of palliative care(11), identified five key domains and developed a draft set of twelve items to capture relevant information on these domains(255). After two rounds of piloting in eight countries, and a meeting of the expert panel to establish content and consensus validity, the list was revised to ten items. Piloting showed the tool was culturally acceptable and brief enough for use in an understaffed health care system.

Rigorous validation of face and construct validity, test/re-test reliability and internal consistency was conducted in five palliative care facilities in Uganda and South Africa(256). Cognitive interviews found good face validity, and qualitative interviews identified that the POS items mapped well onto patients' needs and concerns. Using Spearman's rank test, POS scores were compared with the MVQoLI which had been validated in Uganda(93). Correlation coefficients were low to moderate, reflecting the fact that the tools were developed for different audiences and with different purposes. Cronbach's alpha was 0.6, indicating a moderate internal consistency, which was expected given that the ten-item tool was deliberately multidimensional. Test/re-test reliability was assessed using 342 pairs of observations a mean of two days apart. Intraclass correlation coefficient for the combined score was 0.89 and the lowest score for a single item was 0.78, indicating good reliability.

B.6 Conclusion

HIV is a progressive, life-limiting and incurable condition, and people with HIV experience burdensome multidimensional problems throughout the trajectory of disease. Palliative care is the holistic management of such problems and therefore palliative care is appropriate for people with HIV, as needed. Internationally accepted HIV policy requires palliative care from diagnosis to the end of life(8), which involves detailed assessment and management of symptoms and multidimensional problems. Potential impacts include improved service provision, better patient-reported outcomes, reduced loss to follow-up following diagnosis, improved patient retention in care, hence timely ART initiation and reduced mortality. Most people with HIV in Africa (and hence the majority worldwide) do not receive palliative care.

Better understanding of the problems experienced by people newly diagnosed with HIV is required to deliver appropriate care. The evidence base in Africa is particularly poor, lacking information on prevalence and severity of palliative care-related problems. Knowledge of the prevalence of multidimensional problems at HIV diagnosis is needed, with a patient-centred focus. The APCA African POS is an appropriate tool for the purpose.

C Palliative care-related problems at HIV diagnosis: systematic review

C.1 Introduction

An understanding of needs at HIV diagnosis is essential in order to provide effective, quality care. Research into the problems and palliative care needs of newly diagnosed people has received very little attention. Most studies of palliative care problems in HIV either focus on advanced disease(9) or do not report separately on the individuals recently tested(58). Therefore a systematic review was conducted to identify and appraise the evidence of multidimensional problems at HIV diagnosis, to meet the two goals of informing care provision and identifying gaps in the literature.

C.2 Framing the question

C.2.i Preliminary scoping of the literature

During unsystematic literature searches and reference list searches over a period of eighteen months, a body of literature was identified on the subject of palliative care problems at HIV diagnosis. This literature informed the development of a systematic search strategy. No standard term was in use to describe the newly diagnosed population. In a selection of relevant papers, the simplest descriptive phrases of the population included '*newly diagnosed'*(257, 258), '*recently diagnosed'*(67), '*after the information regarding their HIV status was revealed to them'*(259), '*at the moment of diagnosis'*(260), and '*had recently learned they were HIV positive'*(137). This diversity of descriptions meant that keyword searches would be an impractical means of identifying relevant papers.

Major databases (PubMed, Medline and PsychInfo) did not use any subject heading for recent diagnosis, and more general keywords such as 'diagnosed' returned thousands of irrelevant papers. The lack of consistency in keywords, search terms and descriptions, coupled with the fact that many studies of newly diagnosed people did not identify themselves as such in the abstract, was in itself evidence that the needs of this group have not been clearly defined and that newly diagnosed people have traditionally not been considered a subject of research.

C.2.ii Definition of 'newly diagnosed'

Diagnosis was defined as a patient-centred event; the moment when the patient became aware of their own HIV status. This definition was used to continue the patient-centred perspective of the thesis.

Definitions of 'newly diagnosed' in the literature included those diagnosed within the previous twelve months (261), twelve weeks(67), twelve days(262) or twelve

hours(263). Owing to the paucity of longitudinal studies, the rate of change over problems over time is not known. For the inclusion criteria of the systematic review, ‘newly diagnosed’ was operationalised to mean ‘from the time a patient was informed they were HIV positive to six months later’. Six months was selected because it is common in the literature for observational studies and controlled trials to exclude those diagnosed within the previous six months(264, 265). Similarly, a period of more than six months between HIV diagnosis and entry into HIV care is referred to as delayed care(142, 266).

During data collection, several studies were found which recruited pregnant women who had been diagnosed with HIV during their pregnancy. The category ‘diagnosed during ongoing pregnancy’ was added to the definition of ‘newly diagnosed’. Although ‘during pregnancy’ could extend to nine months, it was thought women were less likely to consent to recruitment into a study in the final weeks of pregnancy, or to have an HIV test in the very first weeks.

C.2.iii Definition of ‘palliative care-related problem’

To focus the systematic review into a specific, manageable question, while maintaining the broad scope of palliative care related problems, seven specific areas of multidimensional burden were identified. These elements were taken from the seven patient-directed items of the APCA African POS(255) (henceforth the POS). The POS is the only multidimensional tool validated for Africa, where two thirds of people with HIV live(14). The POS items were derived from the WHO definition of HIV palliative care, which is the same as that for cancer(11). They cover all four dimensions of palliative care: physical, psychological, social and spiritual.

The purpose of using specific problems was firstly to identify literature which was relevant to the question but outside the context of palliative care, and secondly to ensure that the papers in the review represented problems across the full range of multidimensional patient experience. Preliminary scoping showed that the majority of studies relevant to palliative care problems at HIV diagnosis were not conducted

in the context of palliative care, and that studies of physical symptoms outnumbered those of psychological and spiritual problem, which was not in line with study aims.

C.2.iv Contemporary and retrospective research

Several studies were based on qualitative interviews of people who have been diagnosed with HIV for several years and were asked to recall the experience, either qualitatively(267) or by completing retrospective questionnaires(268). For example, one study asked participants with HIV to compare their present spiritual state with that prior to their diagnosis several years previously, and claimed that an increased interest in spirituality following diagnosis predicted slower disease progression(269). Memory construction research shows that emotionally charged events, such as HIV diagnosis, are remembered with heightened vividness and intensity but impaired accuracy(270).

Another reason to reject retrospective data collection is derived from medical sociology. Illness narrative theory posits that people assimilate damage to physical integrity into their sense of self through constructing a rational narrative out of memories(271-273). According to this theory, accurate emotional recall of the time before HIV diagnosis is likely to be impossible, which invalidates the post hoc instrument completion method (268). In recognition of these problems, studies using retrospective data collection were not accepted for this systematic review. The method can be used to observe the processes of response to biographical disruption(272, 274), including interpretation of HIV diagnosis, but is not an appropriate technique for the study of HIV diagnosis as a lived experience.

C.3 Method

The systematic review method is detailed in full in the published paper(275), included in Appendix E. The method followed the PRISMA recommendations(276).

C.3.i Review question

The primary review question is 'What palliative care-related problems do adults [defined as aged 18 or over] experience at the time of HIV diagnosis?'

This was addressed through seven more specific questions which were taken from the seven patient-completed questions of the POS:

1. What proportion of adults experience pain at the time of HIV diagnosis?
2. What proportion experience other symptoms?
3. What proportion experience worry?
4. What proportion are able to share their feelings?
5. What proportion experience wellbeing?
6. What proportion experience peace?
7. What proportion receive enough help and advice for their family to cope?

C.3.ii Literature identification

The following databases were searched: OVID Medline (1966 to September 2009), PSYCHInfo (1967 to August 2009), Embase (1980 to September 2009) and PubMed. In addition, papers identified through non-systematic means were added if they met the inclusion criteria. There were no limitations regarding study design.

C.3.iii Search strategy

From each POS question item, a word was identified which summarised the patient problems, and these words were used as search terms. Where possible, they were

linked to subject headings, and if no suitable subject heading existed they were used as keywords. The search terms were

- *Pain* – using the accepted palliative care definition that pain is what the patient says hurts(218)
- *Symptoms* - representing physical problems from a patient-centred perspective. Self-reported symptoms have been shown to be more complete and clinically relevant than health provider-reported problems(277)
- *Worry* – representing psychological problems. Worry is a symptom of all anxiety disorders(278) and is frequently associated with depression(279).
- *Wellbeing* – identified in the POS as 'feeling life is worthwhile', and representing QoL and wish to live. In principal components analysis, this question loaded into a factor with items from other scales measuring positive outlook, goals, inner strength, loving, sense of direction, and the beliefs that days have potential and life has value(254).
- *Support* – the family and informal caregivers are important aspects of palliative care. Social support in the literature is divided into two concepts: emotional and tangible/information support. This POS question was correlated against the interpersonal domain of the MVQoLI(256).
- *Peace* - the question 'are you at peace?' is a measure of spiritual wellbeing, validated independently in Uganda, South Africa(256) and the USA(280).
- *Information* - represents informational and tangible support, as distinct from emotional support(281).

Each of the seven subject headings/keywords was combined with *HIV seropositivity* using AND.

The abstracts were read to exclude those papers which did not relate to the newly diagnosed. It was expected that the abstract would not be sufficient to identify all relevant papers, so abstracts were only used to eliminate the clearly irrelevant articles. The results of all seven subject heading searches were combined, with a keyword linking them to the relevant problems area, to remove duplicates. All papers were read and those which met the exclusion criteria were retained for review.

C.3.iv Inclusion and exclusion criteria

The inclusion criteria were:

- Original study (qualitative or quantitative) or review
- Peer-reviewed publication
- Study of people with HIV (any country or group)
- Adults (18 or over)
- Includes at least one of the seven problems
- Not a case study
- English language
- Does not exclude those diagnosed within six months

Exclusion criteria were:

- Analysis group includes people diagnosed with HIV more than six months previously
- Analysis group includes people who are HIV negative
- Analysis group includes people who do not know they are HIV positive
- No results are self-reported measures of patient experience
- Retrospective data collection. For example, a study which asked people four months after diagnosis to recall their experience two weeks after diagnosis would be excluded.
- False positive tests or HIV delusion
- Full paper could not be retrieved(e.g. dissertation abstracts)

The language of palliative care was used to develop the seven search terms, while the great majority of the literature is based in other disciplines which may use different terms to refer to similar concepts. One example which arose in the review process was the term ‘coping’. The theory of coping, developed by Lazarus and Folkman(282), describes the means by which people ‘*deal with demands taxing or exceeding the resources of the person’*(283)(p121). The various responses to stress are defined as negative or positive coping strategies. Many studies of coping strategies in HIV were identified in the review process. Coping, in itself, is not a part of the inclusion criteria, as the aim was to measure patients’ problems and experiences at diagnosis, rather than the means by which they overcame them. In studies of coping, HIV diagnosis alone was used as the variable denoting stress.

C.3.v Data extraction

Data were extracted into a standard proforma. Variables included authors, date of publication, setting, time from diagnosis to data collection, aim, study design, population, tools, analysis, and findings.

C.3.vi Analysis

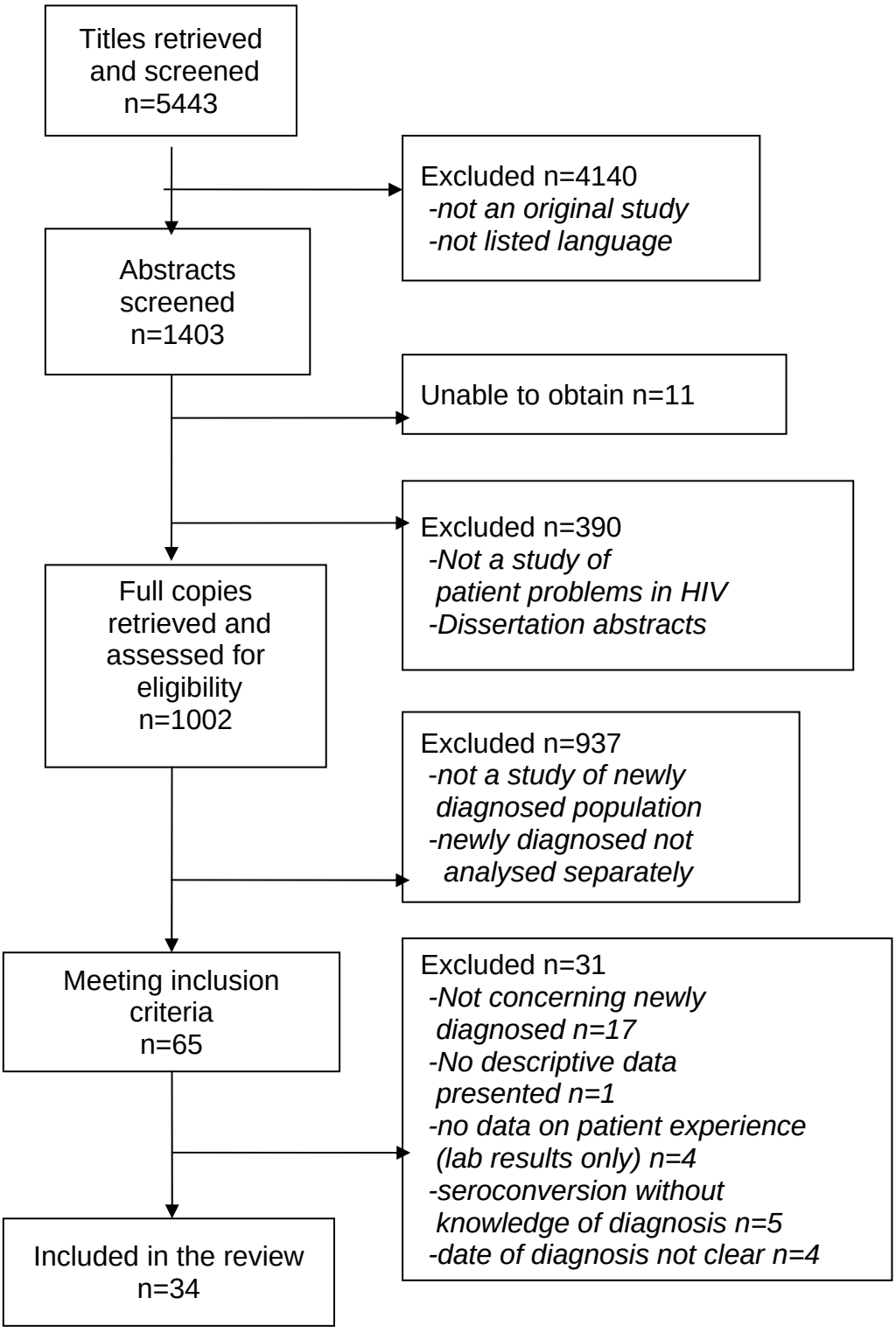
For preference, findings were presented as the percentage of participants to report a problem. Alternatively, mean scores were presented, for example in the case of QoL instruments. The findings in control groups who did not meet the inclusion criteria, and the results of statistical tests comparing the two, were only presented if they were necessary in order to interpret the findings in the newly diagnosed group. In the case of longitudinal studies, findings from all time points which fell within six months after diagnosis were presented. Analysis of change over time was not presented, because it did not answer the review question.

C.4 Results

The search elicited 5443 unique hits (Figure C-1). Review of titles reduced this number to 1403 papers and the abstracts of these were read to identify and exclude papers which were not relevant to the review. Because the default position in the absence of clear information was to retain the paper (an opt-out design rather than opt-in), abstract screening only excluded 390 papers, and 1002 were retrieved in full.

The method section of a paper was often the most useful to assess its relevance, while the abstract and aims could be unclear. Some papers which recruited newly diagnosed participants only made this fact clear in their description of the recruitment process. Sixty-five papers were retained in this way, of which 31 met criteria for exclusion on detailed study, leaving 34 for review.

Figure C-1: PRISMA review flowchart



C.4.i Study designs and methodologies

Seven studies were patient chart reviews and 27 collected primary data. Two papers presented qualitative results(105, 284), and two collected data using in-depth interviews but presented it quantitatively(137, 285). Study designs comprised eleven cohorts (usually with only two or three time points), eight observational cross-sectional studies, two case-control studies, one before-and-after trial, and one RCT. In many cases the research question, analysis and design used in the paper were not all relevant to the review. For seven cohorts, only one time point fell within six months of diagnosis, so these data were presented as cross-sectional. Likewise, only the baseline results from the RCT and before-and-after trial were reported.

Sixteen studies included some element of comparison or control group of people who were not newly diagnosed with HIV. The most common design (seven studies) was a prospective unmatched two-arm cohort, with a newly diagnosed HIV positive group compared to one which was HIV negative. The same comparison was also used in a retrospective record review(286), a cross-sectional survey(287), a matched cohort(288) and a matched case-control study(136). Additionally, two cross-sectional surveys(289, 290) and one prospective cohort(291) compared newly diagnosed participants with people with a pre-existing HIV diagnosis.

One prospective cohort compared newly diagnosed participants who were IDU to newly diagnosed non-IDU(292). Similarly, a case-control study used three control groups to separate the effects of new HIV diagnosis and IDU on health(293). Cases were newly diagnosed IDU; the control groups consisted of newly diagnosed non-injecting men, HIV negative IDU, and HIV positive IDU who already knew their status. For these studies, the results are presented separately for the IDU and non-IDU newly diagnosed groups.

Results from control groups or study arms are only presented if they are needed to interpret the findings in the newly diagnosed group, such as QoL scores, which are essentially comparative. When the outcomes were symptom prevalence or score on a validated instrument with clinical utility, then only results from the newly diagnosed arm are presented.

C.4.ii Populations and settings

Two case-control studies(136, 293) and one two-arm cohort study(292) recruited only patients with recent or current seroconversion. These three were all conducted in high-income countries (Canada and the Netherlands), and measured the prevalence of pain and physical symptoms. Between 13% and 56% of participants were IDU.

Five studies in low-income countries recruited only pregnant women. Three of these used a cohort design(79, 289, 294), but in each case only one time point was within six months of diagnosis, so the results are shown as cross-sectional. The other two pregnancy studies were qualitative(65, 105). Findings covered all areas except the domain of peace. Three further pregnancy studies were conducted in the USA, and measured, respectively, physical symptom prevalence(295), QoL(288), and psychiatric diagnosis(285).

Three studies took place in inpatient settings, all in low- and middle-income countries (the Democratic Republic of Congo, Kenya and Jamaica). All three assessed prevalence of physical signs and symptoms; one in patients with comorbid TB(286), another in patients with comorbid herpes zoster(296), and the third accepting all newly diagnosed inpatients(297). Three further studies took place in low-income countries. Two were analysed as cross-sectional prospective observational studies(298, 299), the other was a retrospective chart review of patients' emotional reactions to HIV diagnosis(300).

There were six studies of outpatients in middle-income countries. Four were cross-sectional prospective observational studies, two using validated outcome measures (287, 301) and two unvalidated(302, 303). The fifth was an observational prospective cohort with validated tools(304) and the sixth was a retrospective chart review of physical symptoms(260).

Finally, eleven studies took place in high-income countries. Seven of them, all based in the USA, predated the introduction of ART in 1996. Perry conducted three prospective cohort studies using structured questionnaires, although only the HIV positive arm of the cohorts was presented in the review(263, 305, 306). Two other

pre-1996 studies also used structured questionnaires to record psychological state as well as symptom burden(307, 308), and one study recorded status disclosure(290). The last used secondary analysis of a prospective cohort to compare newly diagnosed to previously diagnosed people in terms of worry and mood disturbance(291).

Of the four post-1996 high-income country outpatient studies, two used patient records to establish physical symptom prevalence at diagnosis(257, 309) and the others were qualitative studies, of peripheral neuropathy(284) and the experience of a positive HIV test(137).

Table C-1: papers identified in systematic review

Reference ***Year*** ***Country of data collection***	***Study aim*** ***Design*** ***Sample size*** ***Tools***	***Population type*** ***Time from diagnosis to data collection*** ***Analysis***	***Findings*** ***a) pain*** ***b) symptoms*** ***c) worry*** ***d) wellbeing*** ***e) emotional support*** ***f) peace*** ***g) practical support***
Akolo(303) 2008 Nigeria	**Aim:** determine the commonest symptoms and signs at presentation in HIV-infected individuals at a hospital **Design**: cross-sectional prospective study of outpatients at HIV clinic (n=200) **Tools**: a symptom checklist	**Population**: outpatients (middle-income countries) **Time:** 'newly diagnosed'	**b)** 66% weight loss, 42% fever, 39% chronic cough, 32% diarrhoea, 21% oral thrush, 20% wasting,18% lymphadenopathy, 13% pruritus, 13% body rash
Akpaka(286) 2006 Jamaica	**Aim**: determine the prevalence of HIV infection in patients with pulmonary TB at a hospital **Design**: retrospective study of patient records (n=47 HIV+ve, n=359 HIV-ve)	**Population**: inpatients (middle-income countries) **Time**: diagnosed during current hospital stay	**b)** 89% fever, 89% weight loss, 47% dry cough, 21% diarrhoea
Alger(295) 1993 USA	**Aim**: assess the influence of HIV infection on pregnancy outcomes and effect of pregnancy on short-term course of HIV infections **Design**: Two-arm prospective cohort. Data for HIV +ve arm during pregnancy presented only(n=101)	**Population**: Pregnancy (high-income countries) **Time**: diagnosed during current pregnancy	**b)** 28% genital candida, 13% condylomata, 12% oral herpes, 12% fatigue, 11% night sweats, 11% genital ulcers, 9% weight loss, 5% genital herpes
Antelman(79) 2007 Tanzania	**Aim**: examine the burden of depressive symptoms among HIV+ve women (n=996) **Design**: prospective cohort embedded in RCT (only 1 data point within 6 months of diagnosis) **Tools**: subscale of Hodgkins Symptom Checklist-25	**Population**: pregnancy (low-income countries) **Time**: mean 2.5 months after diagnosis	**c)** 43% depressed
Antoni(307) 1991 USA	**Aim**: assess changes in psychological distress, plasma cortisol and blastogenic responses following serostatus notification, to examine disparity between psychological and immune responses evident in HIV+ve individuals **Design**: Prospective two-arm cohort of HIV+ve (n=25) and HIV-ve (n=46) gay men **Tools**: Impact of Events Scale (IES),	**Population**: outpatients (high-income countries) **Time**: 2, 3 and 5 weeks after diagnosis **Analysis**: means presented. Higher score = worse symptom	**c)** STAI state anxiety: 2 wks 43.3, 3 wks 39.7, 5 wks - POMS anxiety: 14.8, 11.7, 11.9 POMS depression: 17.8, 15.8, 11.7 IES intrusion: 20.7, 17.8, 12.9 IES avoidance: 13.6, 14.7, 11.1 IES total: 34.3, 32.5, 24.0

Reference *Year* *Country of data collection*	*Study aim* *Design* *Sample size* *Tools*	*Population type* *Time from diagnosis to data collection* *Analysis*	*Findings* *a) pain* *b) symptoms* *c) worry* *d) wellbeing* *e) emotional support* *f) peace* *g) practical support*
	State/Trait Anxiety Inventory(STAI), Profile Of Mood States (POMS)		
Boyd(257) **2005** **UK**	**Aim**: Establish whether there are ethnic differences at HIV diagnosis in demographic characteristics, disease stage and reasons for testing **Design**: Retrospective study of patient records (n=494)	**Population**: outpatients (high-income countries) **Time**: within 3 months after diagnosis	**b)** 'symptomatic': 35% of whites, 30% black Africans, 25% black Caribbeans. Tested because of symptoms: 19% of whites, 37% black Africans, 31% black Caribbeans
Burchell(136) **2003** **Canada**	**Aim**: understand the circumstances surrounding HIV testing among recent seroconverters (n=80) compared to HIV-ve controls **Design**: Retrospective case-control. Controls matched by gender, HIV exposure and geographic region	**Population**: seroconversion (high-income countries) **Time**: median 3 months since diagnosis	**a)** Of the 66% with symptomatic primary HIV infection (SPHI), 62% had severe headache **b)** 43% tested because of symptoms or illness, 8% because of STD diagnosis Of the 66% (n=53) with SPHI, 100% had fever, 98% fatigue, 96% myalgia, 85% night sweats, 79% diarrhoea, 78% nausea
Chandra(301) **1998** **India**	**Aim**: study factors related to anxiety, depression and suicidal ideation among HIV+ve heterosexuals soon after being tested for the first time **Design**: Observational cross-sectional study (n=51) **Tools**: Hospital Anxiety and Depression Scale (HADS), VAS for pain, psychiatric interview	**Population**: outpatients (middle-income countries) **Time**: 4-6 weeks after diagnosis	**a)** 31% severe pain **b)** 55% painful symptoms **c)** 36% anxiety disorder, 40% depressive disorder **d)** 20% death wish, 12% occasional suicidal ideation, 8% attempted suicide **e)** 43% consider family indifferent, unsupportive or hostile
Conley(291) **1999** **USA**	**Aim**: Evaluate the effectiveness of avoidance of serostatus information as a coping strategy by examining psychological wellbeing of gay men before and after they learned the results of an HIV test. **Design**: Secondary analysis of prospective two-arm before & after study. Only HIV+ve results presented (n=45 newly diagnosed) **Tools**: POMS, Hopelessness Scale	**Population**: outpatients (high-income countries) **Time**: within six months of diagnosis **Analysis**: higher score= worse result	<u>New diag</u> <u>Prior diag</u> <u>Notes</u> **c)** Concern about developing AIDS 3.76 3.55 Max=7 **c)** Subjective risk & lack of control 4.13 3.97 Max=7 **c)** Mood disturbance 17.3 29.9 **f)** Hopelessness 3.7 4.5
Davis(308) **1995** **USA**	**Aim**: examine long term changes in psychological symptomology from 6 to 24 months after notification of HIV+ve serostatus among injection drug users (IDU)	**Population**: outpatients (high-income countries) **Time**: within 6 months after diagnosis for 15/16	<u>+ve</u> <u>-ve</u> <u>Test</u> **b)** SCL-90 58.6 60.0 t=0.1, p=0.9 **c)** BDI 15.4 13.5 t=0.5, p=0.6

Reference *Year* *Country of data collection*	*Study aim* *Design* *Sample size* *Tools*	*Population type* *Time from diagnosis to data collection* *Analysis*	*Findings* *a) pain* *b) symptoms* *c) worry* *d) wellbeing* *e) emotional support* *f) peace* *g) practical support*
	Design: two-arm prospective cohort (HIV+ve IDU n=16, HIV-ve IDU n=81). First data point presented only **Tools**: Symptom Checklist-90 (SCL-90), Beck Depression Inventory (BDI)	**Analysis**: means presented, t-tests by reviewer	
Fitzgerald (300) **2004** **Haiti**	**Aim**: determine whether information collected at HIV notification during VCT can predict patients' future adherence **Design**: retrospective study of patient records (n=1168)	**Population**: outpatients (low-income countries) **Time**: on day of diagnosis	**b)** 26% recorded HIV symptom free **c)** emotional reaction: 42% acceptance, 35% shock, 31% resigned, 16% sadness, 14% denial, 10% fear, 5% tearful **f)** 2% angry
Galati(309) **2005** **Italy**	**Aim**: Describe prevalence and determinants of HIV infection among low-risk subject seeking their first test **Design**: Retrospective study of patient records (n=64)	**Population**: outpatients (high-income countries) **Time**: data collected during pre- or post test counselling	**b)** 7% tested because of alarming symptoms
Hult(137) **2009** **USA**	**Aim:** describe the experience of testing positive for HIV **Design**: qualitative interviews (n=50)	**Population:** outpatients (high-income countries) **Time:** mean 6.7 weeks since diagnosis	**b)** 8% physical response to diagnosis (dry mouth, dizziness, sweating, cognitive impairment) **c)** 32% felt shock/surprise at diagnosis. 14% sadness, depression or crying on diagnosis. 2% felt relief **d)** 4% felt suicidal **e)** 14% said health provider (HP) provided emotional support at diagnosis. 14% said HP's delivery of result was distressing. 10% said HP was very encouraging. 10% said HP was upset
James(285) **1988** **USA**	**Aim**: describe psychosocial problems encountered in patients referred for psychiatric evaluation during pregnancy following HIV diagnosis **Design**: retrospective study of patient records (n=15)	**Population**: pregnancy (high-income countries) **Time**: 13/15 diagnosed during current pregnancy	**c)** 14 have psychiatric diagnosis (8 adjustment disorder, 8 antisocial personality, 6 borderline personality, 1 dysthymia, 1 cyclothemia, 1 major depression, 1 R/O borderline intellect). 3 modd disorder, 11 unstable personality, 13 drug/alcohol abuse or dependence, 4 attempted suicide before
Keogh(65) **1994** **Rwanda**	**Aim**: describe specific HIV-related needs of a sample of HIV+ve women and describe impact of HIV in their lives over a period of time **Design**: repeated in-depth qualitative interviews (n=55). Data from post-diagnosis	**Population**: pregnancy (low-income countries) **Time**: at post-test counselling	**c)** Most pressing concern: 43% childcare. 80% said HIV status caused a great deal of concern **d)** 94% glad to know their test result **e)** 24% thought partner would be supportive, 46% not sure. 35% said neither partner nor family would

Reference ***Year*** ***Country of data collection***	***Study aim*** ***Design*** ***Sample size*** ***Tools***	***Population type*** ***Time from diagnosis to data collection*** ***Analysis***	***Findings*** ***a) pain*** ***b) symptoms*** ***c) worry*** ***d) wellbeing*** ***e) emotional support*** ***f) peace*** ***g) practical support***
	interview only reported		take in their children if they died. **g)** 73% said relatives could not help with future HIV problems. 94% said no services available outside family. Current needs: 55% housing, 45% employment, 32% money, 30% childcare, 26% insurance, 23% food, 9% transport
Kwalombota (289) **2002** **Zambia**	**Aim**: investigate how pregnancy affects mental health and perceived quality of life (QoL) of HIV+ve women who receive diagnosis when already pregnant (n=40) and those already informed **Design**: Two-arm prospective cross-sectional study **Tools**: a structured questionnaire	**Population**: pregnancy (low-income countries) **Time**: diagnosed during current pregnancy	**c)** 95% at least one somatic manifestation of anxiety, 25% poor concentration and lethargy **d)** 100% continuous suicidal thoughts, 95% lost interest in life and felt worthless
Larrabee(288) **1996** **USA**	**Aim**: describe perceived QoL and functional status of women with HIV during the antenatal, perinatal and postpartum periods **Design**: Two-arm observational cohort. HIV+ve pregnant women (n=21) matched on age, race, parity, education to HIV-ve pregnant women (n=21). First data point only presented. **Tools**: MOS-SF	**Population**: pregnancy (high-income countries) **Time**: diagnosed during current pregnancy **Analysis**: median scores presented, Wilcoxon signed-rank tests	<u>+ve</u> <u>-ve</u> <u>Test</br>**a)** pain 66.6 66.6 p>0.05 **b)** physical function 77.8 83.3 p>0.05 fatigue 54.2 58.3 p>0.05 **c)** mental health 56.7 66.6 p>0.05 cognitive function 75.0 71.2 p>0.05 **d)** overall health 60.0 60.0 p>0.05 QoL 60.0 80.0 p>0.05 Health distress 50.0 87.5 p<0.01 **g)** role function 100 100 p>0.05 social function 100 66.6 p>0.05
MacNeil(299) **1999** **Tanzania**	**Aim**: examine differences in sexual risk reduction among newly diagnosed people with HIV who receive care and support, compared to regular services **Design**: RCT of enhanced care and support services. Baseline data presented (n=154)	**Population**: outpatients (low-income countries) **Time**: 4 weeks after post test counselling	**b)** 33% tested because of symptoms, 35% STD symptoms at baseline, 23% genital sores **e)** 19% had disclosed at baseline
Maman(105) **2009** **Democratic Republic of Congo**	**Aim**: Understand ways in which people living with HIV in Africa turn to religion for support **Design**: in-depth cross-sectional qualitative interviews, n=40	**Population**: pregnancy (low-income countries) **Time**: diagnosed during current pregnancy (those quoted)	**e)** disclosing to church pastor initially helped to disclose to partner **f)** Women received support from religious beliefs and practices after HIV diagnosis

Reference *Year* *Country of data collection*	*Study aim* *Design* *Sample size* *Tools*	*Population type* *Time from diagnosis to data collection* *Analysis*	*Findings* *a) pain* *b) symptoms* *c) worry* *d) wellbeing* *e) emotional support* *f) peace* *g) practical support*
Mansergh (290) **1995** **USA**	**Aim**: to assess self-disclosure of HIV+ve serostatus among asymptomatic and symptomatic men who vary in length of time since diagnosis. **Design**: cross-sectional observational study. Results for newly diagnosed group presented (n=79)	**Population**: outpatients (high-income countries) **Time**: 2-4 months after diagnosis	**b)** 27% (n=21) self-reported 'symptomatic' stage **e)** Symptomatic group: 100% disclosed status to lover (where relevant), 75% friend, 57% mother, 28% father, 43% sister, 39% brother, 10% none of above. Asymptomatic group: 75% disclosed to lover, 58% friend, 32% mother, 7% father, 28% sister, 19% brother, 21% none of above
Mientjes(293) **1993** **Netherlands**	**Aim**: study the clinical symptoms associated with HIV seroconversion (SC) among IDU **Design**: Case-control. Cases were SC IDU (n=18), controls SC MSM (n=27), HIV-ve IDU and long term HIV+ve IDU. Data presented for the 2 SC groups	**Population**: seroconversion (high-income countries) **Time**: within 6 months after diagnosis	**a)** IDU: 11% pain with swallowing, 11% headache. MSM: 26% pain swallowing, 15% headache **b)** IDU: 22% tiredness, 33% fever, 11% night sweats, 28% bacterial pneumonia, 28% skin abscess. MSM: 30% tiredness, 48% fever, 19% night sweats
Montessori (292) **2000** **Canada**	**Aim**: Describe clinical and virological characteristics of acute/early HIV infection **Design**: Two-arm prospective cohort study comparing newly diagnosed IDU (n=33) and non-IDU (n=26). Symptoms reported at baseline only.	**Population**: seroconversion (high-income countries) **Time**: within six months of seroconversion	**a)** IDU: 58% headache. Non-IDU: 28% headache **b)** IDU: 65% pharyngitis, 50% lymphadenopathy, 81% fever, 58% rash, 73% anorexia, 54% diarrhoea. Median symptoms 10. Non-IDU: 50% pharyngitis, 44% lymphadenopathy, 53% fever, 28% rash, 25% anorexia, 13% diarrhoea. Median symptoms 4.
Nuwagaba-Biribonwoha (294) **2006** **Uganda**	**Aim**: study the effect of HIV infection on QoL during pregnancy and puerperium **Design**: two-arm prospective cohort study of HIV+ve (n=132) and HIV-ve women. HIV+ve arm results presented here **Tools**: Dartmouth COOP	**Population**: pregnancy (low-income counties) **Time**: 72% diagnosed during current pregnancy **Analysis**: 'poor' = score 3/4 on 0-4 scale	**a)** 28% poor pain score **b)** 76% poor physical fitness score **c)** 12% poor feelings score **d)** 30% poor change in health score, 27% poor overall health score **g)** 36% poor social support score, 15% poor daily activities score, 9% poor social activities score
Olley(287) **2008** **Nigeria**	**Aim**: Examine association of QoL to negative life events, trauma and sexual risk in HIV+ve patients in the air force (n=56) compared with HIV-ve air force personnel (n=69) **Design**: Comparative cross-sectional study **Tools**: MOS-HIV-30, Davidson Trauma Scale for PTSD	**Population**: outpatients (middle-income countries) **Time**: recruited at diagnosis **Analysis**: mean scores presented, t-tests	<u>+ve</u> <u>-ve</u> <u>Test</u> **a)** pain 0.4 0.4 t=-0.3, p=0.8 **b)** phys. function. 7.4 6.3 t=3.1, p<0.05 **c)** PTSD 12.6 4.1 t=5.1, p<0.01 mental function 11.6 8.2 t=4.0, p<0.01 **d)** hlth perception 12.2 11.1 t=1.6, p=0.2 **g)** role function 2.5 2.1 t=2.7, p<0.01 social function 1.8 1.1 t=2.6, p<0.05

Reference ***Year*** ***Country of data collection***	***Study aim*** ***Design*** ***Sample size*** ***Tools***	***Population type*** ***Time from diagnosis to data collection*** ***Analysis***	***Findings*** ***a) pain*** ***b) symptoms*** ***c) worry*** ***d) wellbeing*** ***e) emotional support*** ***f) peace*** ***g) practical support***
Ownby(284) **2007** **USA**	**Aim**: Explore everyday life experiences related to peripheral neuropathy in people with AIDS **Design**: In-depth qualitative interviews using grounded theory (n=19 of whom at least 3 newly diagnosed)	**Population**: outpatients (high-income countries) **Time**: within 6 months after diagnosis for those quoted	**a)** recognising and rationalising neuropathic pain **f)** assimilating annoyance through seeking spiritual meaning in the pain pain interpreted as punishment from God **g)** modifying behaviour, conserving energy, changing activities of daily living (ADL)
Perry(263) **1990** **USA**	**Aim:** to determine the emotional impact of serological testing for HIV **Design:** prospective two-arm cohort. n=39 HIV+ve, n=179 HIV-ve **Tools**: VAS,STAI, Brief Symptom Inventory (BSI), BDI, Hamilton Rating Depression Scale (HRDS)	**Population:** outpatients (high-income countries) **Time**: immediately(T0), 2 weeks(T1) & 10 weeks(T2) after diagnosis **Analysis**: t-tests comparing HIV+ve to HIV-ve at 10 weeks. Data presented for HIV+ve arm only.	**c)** T0 T1 T2 test VAS: mean anxiety 65 43 34 anx: t=2.2, depression 42 27 24 p=0.03 fear of AIDS 68 56 44 fear: t=2.9, fear infecting others 56 47 40 p<0.01 STAI 40.4 36.1 BSI 0.38 BDI 7.4 4.4 HDRS 6.6
Perry(306) **1990** **USA**	**Aim:** to examine the effect of HIV testing on suicidal ideation **Design**: prospective two-arm cohort. n=49 HIV+ve **Tools**: BDI, item 9	**Population:** outpatients (high-income countries) **Time**: 1 week after and 2 months after diagnosis	1 week 2 months **d)** suicidal thoughts 25% 16% suicidal wishes 2% 0 suicidal intent 0 0
Perry(305) **1993** **USA**	**Aim**: measure psychiatric effects of testing for HIV and assess what information feasibly available at intake might predict more severe psychiatric symptoms a year later **Design**: prospective two-arm cohort. Second data point presented for HIV+ve arm only (n=106) **Tools**: HRDS, BDI, BSI, STAI	**Population**: outpatients (high-income countries) **Time**: 6 months after diagnosis	**c)** 20% >13 HRDS 18% >13 BDI 16% >10 BSI 31% >45 STAI state anxiety 28% >45 STAI trait anxiety 48% any of above
Sa(260) **2007** **Brazil**	**Aim:** understand demographic and clinical profile of people presenting with HIV infection **Design:** retrospective chart review (n=377)	**Population**: outpatients (middle-income countries) **Time:** 'the moment of diagnosis'	**b)** 47% asthenia, 44% cachexia, 32% fever, 31% anaemia, 25% persistent dermatitis, 24% oral thrush, 17% diarrhoea, 16% pulmonary TB, 13% persistent cough, 6% herpes zoster

Reference ***Year*** ***Country of data collection***	***Study aim*** ***Design*** ***Sample size*** ***Tools***	***Population type*** ***Time from diagnosis to data collection*** ***Analysis***	***Findings*** ***a) pain*** ***b) symptoms*** ***c) worry*** ***d) wellbeing*** ***e) emotional support*** ***f) peace*** ***g) practical support***
Srisurapont (304) 2001 Thailand	**Aim**: examine the impact of HIV+ve results on HRQoL and social support **Design**: observational prospective cohort (n=30 at week 12, n=27 at week 24) **Tools**: Social Relationship Scale(SRS), Quality of Life Index (QL-Index)	**Population**: outpatients (middle-income countries) **Time**: 12 weeks and 24 weeks post-diagnosis **Analysis**: means presented, t-tests conducted by reviewer	12 wks / 24 wks / Test **d)** QL-Index 9.80 / 9.74 / t=0.27, p=0.79 **e)** SRS-Q 7.35 / 9.01 / t=-1.02, =0.31 SRS-EN 16.57 / 19.30 / t=-0.75, =0.46
Strecker(297) 1994 DRC (Zaire)	**Aim**: assess predictive value of WHO case definition for HIV **Design**: retrospective study of patient records (n=183)	**Population**: inpatients (low-income countries) **Time**: diagnosed during current hospital stay	**b)** 70% weight loss, 36% diarrhoea for >1 month, 53% fever, 25% cough and TB, 19% pruric dermatitis, 17% herpes zoster, 14% polylymphadenopathy, 5% oral candidiasis
Tyndall(296) 1995 Kenya	**Aim**: determine clinical features, degree of immunosuppression, and prevalence of HIV associated with herpes zoster **Design**: prospective observational study(n=196)	**Population**: inpatients (low-income countries) **Time**: diagnosis within a week for 193/196	**a)** 69% severe pain **b)** 57% fever, 14% cough, 9% rash other than zoster, 8% weight loss, 6% diarrhoea, 2% oral thrush.
Wakeham(298) 2010 Uganda	**Aim:** measure symptom burden prior to starting ART in adults presenting for HIV care with CD4<200 (n=212) **Design**: cross-sectional survey as part of double-blinded RCT **Tools**: MSAS-SF	**Population:** outpatients (low-income countries) **Time:** 'at the time of initial HIV testing and diagnosis'	**a)** 76% pain **b)** 70% weight loss, 67% itching, 61% drowsy/tired, 61% lack of energy, 57% numbness/tingling in hands/feet, 53% cough, 52% skin changes, 49% lack of appetite, 43% dizziness, 42% problems with sexual interest/activity **c)** 51% worry, 47% feeling sad **g)** 46% hunger
Wig(302) 2008 India	**Aim**: Describe multidimensional health-related issues of HIV+ve patients **Design**: cross-sectional study with convenience sampling, n=138 **Tools:** a structured questionnaire	**Population**: outpatients (middle-income countries) **Time**: within 2 weeks after diagnosis	**a)** 53% problems due to pain, 44% suffering due to body pain **b)** 96% lack of energy, 40% active TB, 22% oral candidiasis, 20% persistent diarrhoea **c)** 99% emotional problems **d)** 92% problems related to health perception, 68% unhappy most of the time **f)** 58% not feeling calm and peaceful a source of high distress **g)** 54% problems with job or household work

Table C-2: findings in the domains of pain and physical problems, tabulated by population group in which problems were recorded

	Seroconversion (high-income countries)	***Inpatients (low-income countries)***	***Inpatients (middle-income countries)***	***Outpatients (low-income countries)***	***Outpatients (middle-income countries)***	***Outpatients (high-income countries)***	***Pregnant (low-income countries)***	***Pregnant (high-income countries)***
Pain	IDU: 11-58% headache Non-IDU: 15-62% headache	69% severe pain (comorbid herpes zoster)		76% of patients with AIDS	31-53% Comparative: Low pain in air force, not associated with HIV	Rationalising and seeking meaning in neuropathic pain	28% poor pain score (=severe pain)	Pain not associated with HIV
Physical	IDU: 73% anorexia 65% pharyngitis 33-81% fever 58% rash 54% diarrhoea 22% tiredness Non-IDU 48-66% fever 30-65% tiredness 51% nausea 50% pharyngitis 19-56% night sweats 13-52% diarrhoea 28% rash 25% anorexia 43% tested because of symptoms	53-57% fever 67% itching 8-70% weight loss 25% active TB 14% cough 6-36% diarrhoea 9-19% skin problems 2-5% oral thrush	89% fever 89% weight loss 47% cough 21% diarrhoea	70% weight loss 67% itching 61% tiredness 53% cough 52% skin problems 49% cachexia 35% STD symptoms 74% 'symptomatic' 33% tested because of symptoms	47-96% tiredness 66% weight loss 55% 'painful symptoms' 44% cachexia 32-42% fever 13-39% cough 13-25% skin problems 16-40% active TB 17-32% diarrhoea 21-24% oral thrush 27% 'symptomatic' 7% tested because of symptoms Comparative: Lower physical function associated with HIV status	8% had physical response to diagnosis Symptoms burden not associated with HIV for IDU 19% of whites and 37% of black Africans 'symptomatic'	76% poor physical fitness	41% female problems 12-41% low energy 28% difficulty eating 28% genital thrush 25% vision problems 13% condylomata 12% oral herpes 11% night sweats 9% weight loss Physical function and fatigue not associated with HIV

Table C-3: findings in the five domains of non-physical problems, tabulated by population group in which problems were recorded

	Outpatients (low-income countries)	***Outpatients (middle-income countries)***	***Outpatients (high-income countries)***	***Pregnant (low-income countries)***	***Pregnant (high-income countries)***
Psychological	47% depressed 51% worried 42% responded to diagnosis with acceptance, 35% shock, 31% resignation, 16% sadness, 14% denial	36% worried 40% depressed 99% emotional problems PTSD and low mental function associated with HIV	18-20% depression 32% said primary response was shock, 14% sadness Anxiety, depression and fear declined over 5-10 week period Depression not associated with HIV	80% said HIV status caused a great deal of concern 12% low feelings score 95% at least 1 somatic manifestation of worry	41% problems thinking, 41% risk of depression Comorbidities include AD, ASPD, BPD Mental health, cognitive function and depression not associated with HIV
Wellbeing		8% attempted suicide 12% suicidal ideation 20% death wish 68% unhappy most of the time 92% problems related to health perception Health perception not associated with HIV QoL does not change between 12 and 24 weeks after diagnosis	4% felt suicidal at diagnosis 24% suicidal thoughts after 1 week 16% suicidal thoughts after 2 months	100% suicidal thoughts 95% lost interest in life 27% poor overall health 30% poor change in health 94% glad to know their test result	Mean perception of health is average Overall health and QoL lower in HIV+ve group but not associated with HIV
Emotional support	19% had disclosed status after 4 weeks	43% considered family unsupportive, hostile or indifferent Social relationship quality does not change from 12 to 24 weeks after diagnosis	14% said health provider provided emotional support 14% said health provider added to distress Men with symptoms were more likely to disclose their status	Disclosing to pastor helped women disclose to their partner 24% thought partner would be supportive 46% not sure whether partner would be supportive 35% said family/partner would not take their children in if they died	
Peace	2% angry at diagnosis	58% highly distressed by not being calm or peaceful	Seeking spiritual meaning in pain to assimilate annoyances	Women received support from religious beliefs and practices	

	Outpatients (low-income countries)	***Outpatients (middle-income countries)***	***Outpatients (high-income countries)***	***Pregnant (low-income countries)***	***Pregnant (high-income countries)***
Information/ tangible support	46% of people with AIDS report hunger	54% report problems with household or work HIV associated with more limited role function and social function	Modifying behaviour, conserving energy, changing ADL to reduce neuropathic pain	73% said relatives could not help with future HIV problems. Current needs: 55% housing, 45% employment, 32% money, 30% childcare, 23% food. Most pressing need: 43% childcare 36% poor social support, 15% poor daily activities, 9% poor social activities	Role function and social function not significantly associated with HIV 19% have limited physical function in walking uphill 16% limited at work 6% limited ADL

C.4.iii Pain (11 studies)

Table C-2 displays the findings in the domains of pain and physical problems, by population group. In prospective observational studies, pain prevalence ranged from 31% to 53% in middle-income country outpatient populations(301, 302), and was 76% among patients with AIDS(298) and 69% for inpatients with comorbid herpes zoster(296). In comparative studies, HIV infection was not a significant risk factor for pain(287, 288). Two studies of seroconversion compared prevalence of specific types of pain (e.g. headache) between IDU and non-IDU(292, 293), but the sample sizes were too small to draw any comparative conclusions.

In qualitative interviews, patients with neuropathic pain described a three-stage process: isolating the symptom cluster, inventing/testing management strategies, and assimilating annoyances. The first stage involved recognition, interpretation and rationalisation of the new symptoms of neuropathic pain. Secondly, participants modified their behaviour, for example planning energy conservation and changing their activities of daily living(ADL). Third, the annoyances of neuropathic pain became assimilated through acceptance of the differences and a search for spiritual meaning in the pain(284). Some newly diagnosed participants would catastrophise, interpreting their pain as a sign of advanced disease and imminent death. As predicted by the Theory of Unpleasant Symptoms(310), patients more anxious about their symptoms reported more severe pain.

The variables “problems due to pain” and “suffering due to body pain” may represent the phenomenon of “total pain”. Saunders described how multidimensional problems such as anxiety and isolation can be inseparable from physical pain. The qualitative evidence illustrates this principle. The physical pain of neuropathy was exacerbated by the psychological and spiritual meanings attached to it(284). The newness of the symptom, as something outside normal experience, also added to the distress it caused.

C.4.iv Physical problems (22 studies)

The largest number of studies (n=22) recorded physical symptoms and infections. Many did not specify symptoms, and none reported on severity of individual symptoms. Physical symptoms were highly prevalent in low- and middle-income countries. Prevalence information from high-income countries was confined to pregnant women or recent seroconverters. Common symptoms in outpatient studies included tiredness(47-96%), weight loss(66-70%), fever(32-42%) and skin problems(13-52%).

Weight loss, fever, cough and diarrhoea were the most common symptoms in four low- and middle-income country prevalence studies(286, 296, 297, 303), but their prevalence varied widely. For people with AIDS in Uganda, the most prevalent symptoms were weight loss, itch, tiredness and lack of energy(298). High frequencies of sexually transmitted infection (STI) symptoms were also noted among newly diagnosed participants in Tanzania (299). In India, 96% of a convenience sample reported lack of energy, 40% TB and 20% diarrhoea(302). In Brazil, the most common symptoms were asthenia, cachexia, fever and anaemia, but TB, diarrhoea and cough were recorded for more than 10% of patients(260).

In pregnancy, fatigue and STIs were often measured. Pregnant women in the USA reported fatigue, night sweats and weight loss, and a number of STIs, not necessarily symptomatic(295). Pregnant women in Uganda reported poor physical fitness score in 76% of cases on the Dartmouth COOP scale(294).

In comparative findings, HIV was associated with impaired physical function for air force personnel in Nigeria(287), but not for pregnant women in Uganda(288). HIV did not affect the symptom experience of IDU in the USA(308), but in Canada, HIV positive IDU reported more symptoms than HIV positive non-IDU, suggesting that drug use had more effect than HIV on symptom burden(292). IDU more frequently reported fever (81%), anorexia(73%) and diarrhoea(54%). By contrast, in the Netherlands non-IDU had the higher symptom burden for fever and tiredness at seroconversion(293).

Three papers used the undefined categories ‘symptomatic’ and ‘asymptomatic’ HIV(257, 290, 300). These terms are derived from the surveillance definition of HIV and AIDS, not the clinical definition (311-313). This classification distinguished between HIV infection with and without case-defining symptoms, but regressed into general use of the word ‘asymptomatic’ to describe pre-AIDS HIV(248, 314). The risk of ‘symptomatic’ status at diagnosis was 74% according to patient records in Haiti(300), and a self-reported 27% in a small prospective study in the USA(290).

The only information on physical symptoms in high-income countries, apart from patients with either seroconversion or pregnancy, was derived indirectly from asking patients their reason for an HIV test. In Canada, 43% of recent seroconverters tested because of symptoms or illness(136), compared to 33% of the HIV positive population in Tanzania(299). In the UK, patient records showed that 37% of black Africans and 19% of whites tested after symptoms(257). Finally, HIV diagnosis could itself be a cause of symptoms such as sweats, dry mouth and dizziness(137).

C.4.v Psychological problems (17 studies)

Table C-3 has five columns rather than the eight in Table 2, because no results in any of the non-physical domains (i.e. psychological, wellbeing, spiritual, emotional or informational/tangible support) were found for inpatients or people with recent seroconversion.

For low-income country outpatients, anxiety and depression prevalence were high (51-95% and 47% respectively). In middle-income countries, anxiety and depression were less prevalent but still high, and 99% of an Indian sample reported emotional problems (302). In the USA, 28% scored above the threshold in terms of trait anxiety and 18% for depression(305).

Two studies with outlier results were methodologically weak; one problematically translated ‘emotional health’ to ‘feelings’ and then to ‘mental state’(294), the other failed to describe any instrument or symptom checklist(289). One study recruited

only participants who were referred for psychiatric evaluation. The fact that 14 of the 15 had a psychiatric diagnosis is not representative of an average population, although it illustrates the range of psychiatric conditions comorbid with HIV(285).

Four comparative studies made use of psychological measures. The largest, in Nigeria, found post-traumatic stress disorder and lowered mental health were associated with HIV(287). In the three smaller studies, all in the USA, HIV status was not associated with mental health using the MOS-SF(288) or the BDI(308), and it was not possible to determine whether a difference in 'subjective risk and lack of control' was significant either clinically or statistically(291).

In the USA 32% said in qualitative interviews that their primary response to diagnosis was shock while 14% felt sad and depressed(137). The same question was addressed using patient records in Haiti, where recorded reactions were shock(35%) and resignation(31%)(300). Prevalence of anxiety, depression, intrusive thoughts and fear appeared to decline over time in two American cohorts. However, one did not include statistical analysis(307), and the other used it inappropriately(263). Furthermore, the first study excluded patients with common physical HIV symptoms, which biased the cohort towards a generally (and therefore psychologically) less morbid population(307).

C.4.vi Wellbeing problems (10 studies)

The evidence revealed widespread unhappiness and loss of wellbeing. The largest prospective observational study to include wellbeing, in India, found that 92% experienced problems related to health perception, and 68% were unhappy most of the time(302). In Uganda, 27% of pregnant women reported poor overall health(294).

Three papers reported on suicidal thoughts, with widely variable results. In India, 8% of participants reported they had attempted suicide in the week after learning their HIV status, and 20% reported death wish(301). Seven weeks after diagnosis, two of 50 people in an American sample felt suicidal(137). One study reported

continuous suicidal thoughts by all participants, but failed to describe a credible method(289).

Cohort studies did not identify a significant change in wellbeing over time (304). The prevalence of suicidal thoughts in a USA study reduced non-significantly(306). The single comparative study of wellbeing found that HIV was associated with greater health distress in pregnancy but there was no difference in QoL(288).

C.4.vii Emotional problems (7 studies)

Evidence of need for emotional support included studies of disclosure of HIV status or expected response to disclosure. The evidence showed that participants were very concerned about the reactions of their families. In Rwanda, 24% of women thought their partner would not be supportive after they disclosed their HIV status and 46% were not sure(65). Similarly, in India 43% of participants recorded their family indifferent, unsupportive or hostile(301). It was not clear how the question was worded and whether these emotions were directly quoted or extrapolated from expected actions. Two to four months after HIV diagnosis in the USA, 21% of self-described ‘asymptomatic’ men had not disclosed their status to their partner or close family while 90% of ‘symptomatic’ men had done so(290). In qualitative interviews in the DRC, some women described how disclosing their status to their church pastor first had given them the confidence to disclose to their partner(105).

C.4.viii Spiritual problems (5 studies)

In India, 58% of participants reported that not feeling calm and peaceful was a source of high distress for them(302). A comparative study from the USA measured hopelessness but not enough context was presented to allow interpretation of the results(291). A review of 1168 patient records in Haiti showed that 2% of participants responded to their HIV diagnosis with anger(300).

The paper on the role of religion in women's lives in the DRC was written after 38 of 40 women spontaneously mentioned religion in qualitative interviews(105). Women reported shock, sadness and anger at HIV diagnosis, and described the use of prayer, the Bible and support from the church to overcome these feelings. There were no reports of women who refused treatment because of religious belief, but some gained hope from the belief that God would cure them because they were innocent. An alternative view was expressed by women who found peace in understanding that 'God had chosen this path for them'(105). Two spiritual reactions to neuropathic pain emerged in qualitative interviews(284). One, adopted only by the newly diagnosed, was to interpret the pain as punishment from God for past actions. The second response was to 'reach beyond', and draw inner strength from a spiritual connection.

C.4.ix Information/tangible support problems (7 studies)

In many contexts, people with HIV were limited in their work, activities and support. There was limited evidence of HIV as a risk factor from comparative studies.

In Rwanda, 94% of a sample of pregnant women in the capital city were not aware of any support services outside the family and 73% said their family would not be able to help in the future, usually because of age, poverty or distance(65). Their main reported needs were housing, employment, money, childcare, insurance and food, with childcare the most pressing concern for 43%(65). In India 54% of participants reported problems with their job or household work(302), and 46% of people with AIDS in Uganda reported hunger(298).

Quality of social relationships was measured with a validated tool at twelve weeks and 24 weeks after diagnosis in Thailand, and did not change significantly according to MANOVA(304). HIV was associated with limitations to role function and social function in Nigerian air force personnel(287), but did not achieve significance for pregnant women in the USA(288), in a much smaller study.

C.5 Discussion

The findings demonstrate a high prevalence of problems across all palliative care dimensions at the time of HIV diagnosis. The evidence is fragmentary, with many studies conducted for reasons other than investigating diagnosis.

C.5.i Situating findings in the literature

This review shows that the prevailing view of the adverse emotional and psychological effect of an HIV diagnosis(305, 315, 316) is based on little evidence. The best evidence of the impact of diagnosis is from a study published 20 years ago, with a total sample of only 69(307), which found high anxiety, depression and intrusive thoughts a week after HIV diagnosis. These symptoms diminished over a four-week period, with less change to anxiety scores. In contrast, data collected in the 1980s showed that anxiety peaked just after HIV diagnosis but fell within a week(263). The reason could be that at that time, HIV was thought to progress to AIDS in only a minority of cases.

Taking an HIV test is a cause of stress. Perry showed in 1990 that suicidal ideation was higher before result notification than after, even for those who were positive(306). In India, 150 people (46% of whom were HIV-positive) about to take a voluntary test had high levels of anxiety, distress and depression, not associated with HIV status(317). When the HIV test was developed there was concern that the negative psychological consequences of knowing one was HIV-positive might outweigh any benefit derived(305). Closed-question studies have shown that fear of the anxiety of knowing positive status and fear of the anxiety of waiting for the result are two of the main reported reasons not to test (318, 319). In Zimbabwe, 96 people referred for an HIV test after presenting with symptoms reacted to the diagnosis with anger, fear, denial, and fatalism. The study concluded that people newly diagnosed with HIV

> *"had a host of social, emotional, and informational needs, which often seriously impeded their capacity to make constructive use of the knowledge of their HIV status*"(258).

In Rwanda, a quarter of women did not expect their partner's support and almost half were not sure of support from their relatives(65). Follow-up interviews three years later showed that in fact the majority of partners were supportive(65). There is evidence that families are more supportive than patients expect(320).

There is increasing concern regarding loss to follow-up (LTFU) of newly diagnosed patients who do not return for care until their disease is far advanced (238, 321). The physical symptoms, worry and depression, loss of wellbeing and sense of meaning, and limited practical support identified in this review might prevent patients receiving care. Palliative care may improve patient retention because of its total care approach and focus on patient experience.

C.5.ii Gaps in the evidence

The majority of identified evidence was confined to physical and psychological symptoms. Evidence of need for emotional support was largely represented by studies of disclosure, which is related to secondary prevention and is not necessarily patient-centred. Almost no quantitative research included spiritual distress, and the topic arose in qualitative research only because the open structure of the method allows participants' concerns to guide data collection. The majority of HIV diagnoses probably take place in a low-income outpatient setting, and yet only three studies recruited from this group, of which one only included AIDS patients(298) and one was a poor-quality chart review(300).

Theories of psychological adjustment and coping suggest that problems may change rapidly(283), and therefore longitudinal studies are important. Although eleven of the 34 studies utilised a cohort design, only four cohorts measured outcomes more than once within six months of diagnosis(263, 304, 306, 307).

The data on problems of inpatients and problems of recent seroconverters related only to physical symptoms and pain. The prevalence of physical symptoms was very high in these groups and it seems likely that psychological, spiritual and social

problems would also have caused burden, but there has been no research in these areas.

C.5.iii Quality of evidence

There were methodological problems with many studies. A major underlying cause of problems was that studies were designed for different purposed. The use of unsuitable, unvalidated or unspecified tools was also common.

1. Study aims

Studies were conducted for a variety of aims, including:

- To study the effect of HIV on QoL in pregnancy(294)
- To identify the clinical characteristics of acute HIV infection(292, 293)
- To determine HIV prevalence among inpatients with TB(286)

The recruitment of people newly diagnosed with HIV was only incidental to these aims. In many cases, careful reading of the methods section of the paper was required in order to identify whether participants were newly diagnosed. The studies did not aim to measure the needs and problems of people newly diagnosed with HIV and thus they were not optimally designed for that purpose. For example, longitudinal studies did not take their starting point from diagnosis, the time since diagnosis is not always clear, and is often too variable for a homogenous sample.

There were methodological problems with many studies. Ten reported symptom prevalence using records completed by care providers, who are known to record only a third of the symptoms reported by patients(54, 277), so they are likely to underestimate patients' problems. The time period within which symptoms were reported was rarely given. No information on symptom severity, duration or distress was recorded in any studies, nor was any association drawn between symptoms and QoL. Sample sizes were small in most prospective studies. The terms 'symptomatic' and 'asymptomatic' were used without definition.

Extraction of information from patient records is a less effective way of obtaining information on symptoms. Firstly, the symptoms and problems identified could consist only of those about which the health worker asked or the patient volunteered information(260). Secondly, HIV service providers identify fewer symptoms than patients(54). Thirdly, inpatient studies are biased towards a higher than average symptom prevalence, because all participants were ill enough to require admission. Reporting quantitative findings from qualitative interviews, as two studies did(137, 285), is generally weak because it does not benefit from the strengths of either method. The population is unlikely to be representative, and at the same time the depth and richness gained from qualitative research is lost.

The four longitudinal studies to have more than one point within the range of the review suffered from several methodological flaws. Analysis techniques were limited to unpaired t-tests and chi squared tests. These tests assume independence between measurements and do not account for the clustering effect within individuals. The use of only two time points did not allow for exploration of the rate of change over time.

2. Use of tools

Several studies did not describe data collection methods in adequate detail. Symptom prevalence information was presented without identification of an instrument used to collect it(136, 295). In other cases, the authors stated that a questionnaire had been developed but it was not presented and had not been validated(302). Without this, the validity and reliability of results cannot be established. This was a particular issue for one study in Zambia(289) which presented 95% prevalence of mental health problems, collected using a new and unvalidated instrument. In another study, when participants were asked to name their most pressing problem, it was not clear whether they picked an option from a closed list or recorded open answers(322). Sometimes the tool was validated in a different setting and cultural context from the study location(287). This was more common for studies in low-income countries, probably because fewer validated tools are available. The range of data collection methods used probably contributed to variation in prevalence figures.

Most studies(n=24) measured outcomes in only one or two domains, rather than taking a holistic view of patients. However, four studies measured outcomes in five domains(287, 288, 294, 301) and one included six(302). These often made use of QoL questionnaires. Quality of life studies aim to reach latent variables rather than directly measure patient experience As a result, a QoL score on its own has little meaning, which is why most QoL studies in the review were comparative.

C.5.iv Limitations of the review

The words chosen for the search strategy were closely linked to the POS, because the review aimed to be patient-centred and the POS is based on patient-reported experience and priorities. In some cases the POS item did not include a single word that encapsulated the intention of the question, and then another word was substituted. For example, ‘feeling life is worthwhile’ was interpreted as ‘wellbeing’. More controversially, ‘having enough help and advice for the family to cope’ was interpreted as ‘information’.

The word ‘worry’ was used for the third item, taken directly from the POS question. An alternative option would have been to use a subject heading such as ‘psychology’, which would have returned every paper on HIV and psychology. This option may seem logical, given that the review findings were ultimately reported under categories including ‘psychological problems’, some of which were depression, sadness and cognitive problems rather than worry. Again, the choice was to be patient-centred, thus to search for evidence of a specific problem (worry) rather than an academic or clinical area (psychological). The review aimed to identify prevalence data on reported problems known to be important to patients. In the event, the findings were displayed in themes which were wider than the original search terms, but the categories followed the data, rather than the other way around.

The choice of words obviously governed the selection of papers and it is a limitation of the systematic review that the keywords were somewhat subjective.

However, the search terms were only used for the initial selection of 5443 papers. The reduction from 5443 down to 34 was based on other exclusion criteria and this stage probably had the greater effect on the findings. The use of other search terms would probably have identified a different, but substantially overlapping, initial group, and since 99.4% of papers were excluded, a great deal of difference could occur to the starting group without having any real effect on the final selection.

It was not always clear when data collection had taken place in relation to diagnosis. For example, one study collected information either during pre-test or post-test counselling, without distinguishing between the two(309). Inpatient chart reviews were sometimes included even though the paper did not state explicitly that patients were newly diagnosed, because logistically they had to have been diagnosed between admission and discharge(286).

The epidemiological, cultural and social environment has not been considered in any depth. Due to the small number of papers, all studies were presented together with no subgroup comparisons. Some studies set comorbidity conditions, such as TB(286), herpes zoster(296) and peripheral neuropathy(284), and one included only patients with a CD4 count below 200(298). In these cases the results are only generalisable to other patients in the same circumstances.

Despite considerable effort, some studies could not be obtained because they were published in small regional journals with limited access. Publication bias may have distorted the findings. Only one researcher appraised the search results and applied the review criteria, as opposed to PRISMA recommendations of two(276). Due to limited time and resources, papers were all in English. However, the review used a broad search strategy and followed established guidance(323).

C.6 Conclusions

Patient-centred research into the experience of HIV diagnosis is scarce, is of mixed quality, and does not represent the majority of people newly diagnosed with HIV. Nonetheless the consistency of evidence for problems in many populations supports the conclusion that severe, distressing, but manageable multidimensional problems are likely among people newly diagnosed with HIV. These problems include pain, worry and depression, social concerns, spiritual distress, lack of information, and impaired wellbeing.

Pain and symptoms, worry, social and spiritual distress and isolation cause unnecessary suffering and should be identified and controlled for that reason alone. Additionally, these problems limit quality of life(324), and impact on people's ability to support themselves(325), make good decisions(326), adhere to treatment(50, 147), and survive(150). All these problems have been identified as highly prevalent and severe in populations with newly diagnosed HIV.

Multidimensional problems can contribute to patient attrition from care(147). The burden of multidimensional problems soon after HIV diagnosis may contribute to the very high loss to follow-up widely recorded in Africa, beginning immediately after HIV diagnosis(157), and responsible for preventable morbidity and mortality(158, 321).

C.6.i Implications for research

The review demonstrates the considerable gaps in the literature describing diagnosis of HIV from the patient-centred perspective. Specific areas where evidence is almost entirely lacking include:

- The first two weeks after HIV diagnosis
- Patient-centred, multidimensional problems
- Severity of problems
- Longitudinal prevalence
- Representative sample of outpatients

- Low-income settings, particularly sub-Saharan Africa
- High-quality and rigorous studies using validated outcome tools

There is some evidence from these studies that HIV diagnosis is a time of many multidimensional problems but the evidence is inadequate for policy making and clinical practice, because it was not collected and analysed with that end in mind. No patient-centred multidimensional longitudinal studies of HIV diagnosis were identified. Very little is known about the change in prevalence or intensity of problems in the first weeks and months after diagnosis. The few longitudinal studies available tend to use widely-spaced time points and crude statistical analysis.

The evidence for experience at HIV diagnosis is patchy, out of date, and unrepresentative, therefore insufficient to create policy or plan effective and appropriate care. We have no knowledge of how soon after diagnosis problems begin, how long they last and whether they change over time. A large scale, methodologically sound, representative cohort study of patient-centred problems at HIV diagnosis is urgently needed to ascertain their prevalence and extent in the time period most relevant to care: the first appointment after an HIV test.

C.6.ii Implications for policy and practice

Diagnosis is by definition the point when HIV care can begin, but for many people the HIV test is both their first and last contact with HIV care services(157). For a patient-centred approach, the priority at HIV diagnosis should be to establish a sustainable relationship with patients and to ensure they have both resources and motivation to return for further care.

HIV palliative care can effectively reduce pain, symptoms and anxiety, and improve insight and spiritual wellbeing(140). From the available evidence it seems likely that multidimensional problems are present from the point of diagnosis. Under current practice many of these are probably not identified, as it is known that HIV symptoms are consistently under-reported(54). If problems are not assessed or recognised then they cannot be managed, nor can effective interventions be

developed for them. The care that is delivered to newly diagnosed HIV patients is not appropriate to their needs. Clinicians and policy makers do not know how to effectively manage multidimensional problems at HIV diagnosis for optimal patient outcomes.

D Aim and objectives of the study

D.1 Aim

To determine the palliative care-related problems experienced by people in Kenya and Uganda in the two weeks following diagnosis of HIV, and how those problems change over the subsequent three months.

D.2 Objectives

In adult outpatients with HIV in Kenya and Uganda:

- To determine prevalence and severity of palliative care-related problems within two weeks of diagnosis
- To investigate whether demographic variables or CD4 count are associated with prevalence and severity of palliative care-related problems at diagnosis
- To determine change in palliative care-related problem severity over a three month period
- To investigate whether demographic variables or ART use are associated with change in palliative care-related problem prevalence over time

The short period of three months is selected because it is apparent from the systematic review that the time closest to HIV diagnosis is the least understood, and a time period of three months rather than six will enable closer study of it.

E Methods

E.1 Design summary

This thesis uses data extracted from an observational prospective cohort collected in 2008. The cohort was part of a Public Health Evaluation (PHE) of the Care and Support component of PEPFAR, a US$15 billion programme aimed at providing HIV prevention, treatment and care over five years. Twelve health facilities participated in the evaluation, six in Kenya and six in Uganda. Each facility consecutively recruited consenting adults diagnosed within the previous 14 days. Data including self-reported QoL, multidimensional problems, and services received were collected at baseline and every following month for three months. The period of 14 days was selected after consultation with health care workers in the field. Testing was done at small clinics or mobile testing centres which would refer positive patients to the facility for care. The 14-day period allowed time for these patients to access the facility.

E.2 Data collection methods

E.2.i Study design

As described above, the study used a prospective multi-centre cohort design, with rolling consecutive recruitment and a three-month follow-up period.

E.2.ii Facility selection

In each country, a random sample of 60 facilities stratified by facility size (in number of patients) was selected from a total of over 600 receiving PEPFAR funding for Care and Support. From the sample of 60, the six with the highest number of patients in the year 2005-2006 were selected for the cohort study. The total sample of 120 facilities was used in a cross-sectional survey. The largest six from each country's random sample were used for the prospective cohort because facilities needed sufficient staff and resources to perform the extra work of the evaluation. The facilities are described in Appendix C.

E.2.iii Participant recruitment and enrolment

Participants were consecutively recruited from January 2008, or when the facility was ready to begin. All patients who met the following criteria were approached:

- 18 years of age or over
- diagnosed HIV positive
- were aware of their diagnosis
- had sufficient cognitive ability to answer the questions for the study
- newly registered at the service

Participants gave informed consent to participate following provision of an information sheet and consent form. These documents were translated into local languages (Swahili, Luo, Runyakitara and Luganda), and were read aloud by the HCW if the participant was nonliterate. Participants were reimbursed travel expenses to the facility of US$5 per visit. The recruitment strategy was modified at each facility to fit it most successfully into the existing care framework. For instance, at some facilities the HIV test results were given by a counsellor who then referred the patient to a nurse. In that case, the counsellor would conduct recruitment and the nurse would administer the questionnaires. In another example of adapting the study to fit the care pathway, at one facility a note was made on the front cover of the file of every patient enrolled in the study, as a reminder to collect their 'patient pack' and complete the questionnaires.

E.2.iv Inclusion criteria for the thesis: defining 'newly diagnosed'

Figure E-1 below shows the decision tree used to identify longitudinal study participants who were defined 'newly diagnosed'. All relevant data were used to make the decision, and any evidence that a participant had been diagnosed HIV positive more than 14 days prior to recruitment was sufficient for exclusion. The date of recruitment for each person was designated 'T0', for Time 0.

The decision to set the limit at 14 days was influenced by the study design and by information on the logistics of patient registration in Uganda and Kenya. Staff reported that facilities were often overburdened and gave newly diagnosed individuals an appointment date several days ahead for their registration (Professor Easterbrook, personal communication). On the other hand, the longitudinal study measures outcomes at monthly intervals, therefore it seemed unreasonable to allow the definition of 'newly diagnosed' to encompass those diagnosed as long as a month ago, which would assume that no change in outcomes had occurred. Fourteen days after HIV diagnosis is the maximum length of time within which the British HIV Association recommends a specialist assessment(262).

Participants were asked directly to give the date when they had been diagnosed HIV positive. When the precise day of the month was not known, 15 was used. Date of ART initiation, where applicable, was obtained in the same way.

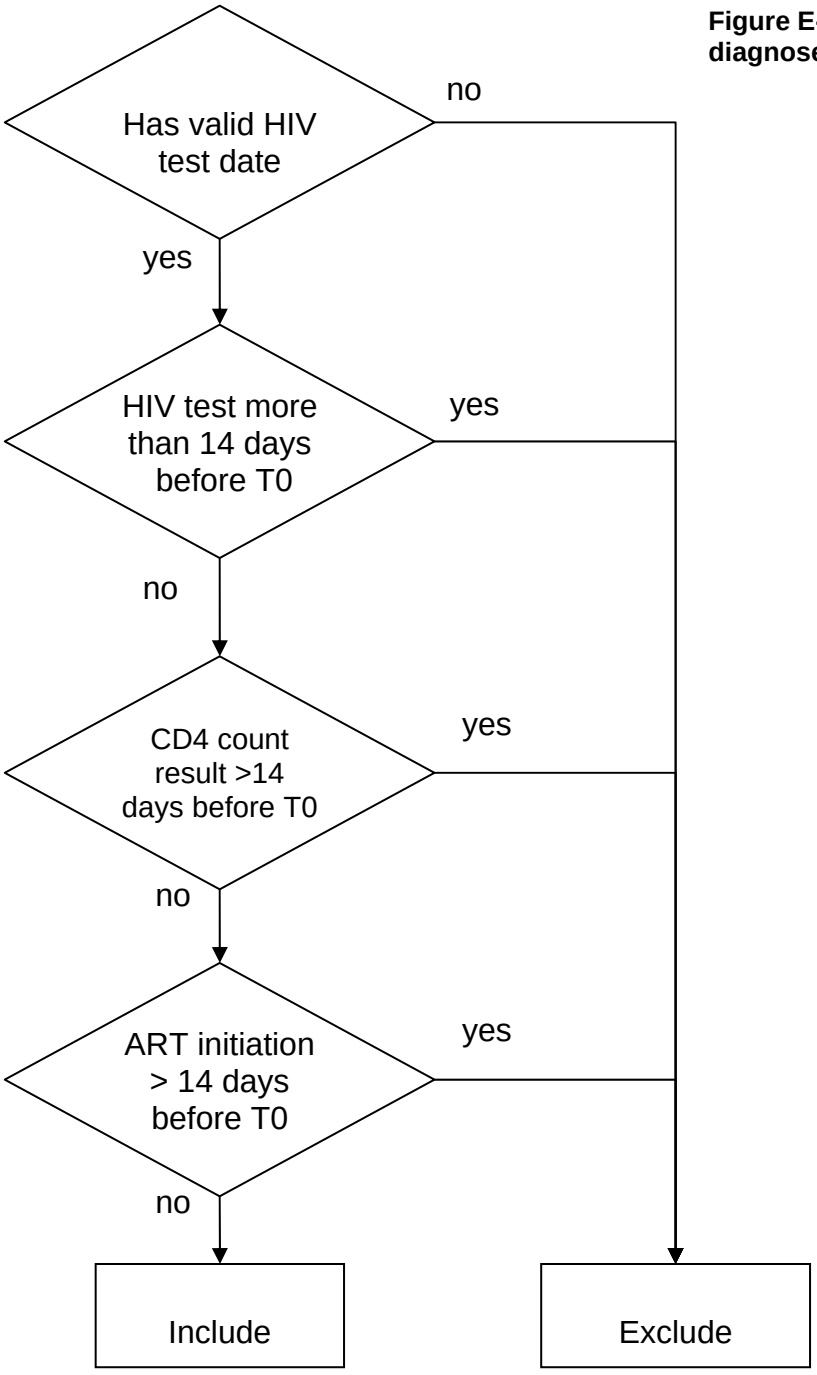


Figure E-1: decision tree to define 'newly diagnosed'

E.2.v Instrument selection and development

The data collection tools for the longitudinal study were four questionnaires, one (demography) used only once per person at baseline and the others used four times at monthly intervals. Two of the questionnaires (the MOS-HIV and CSRI) were not used in this thesis and are not presented here. The time points were designated T0 (entry to the study), T1, T2 and T3. Individual 'patient packs' were created for data collection, consisting of all the tools bound in order, with the pages colour coded by time point, and preceded by a log page containing metadata on progress of data collection and management. The front cover of the pack was blank apart from the patient's name. When the final time point was complete, this page was torn out, making the data unidentifiable.

For each facility, questionnaire packs were prepared in two languages; English and the most common local language (Swahili, Runyakitara, Luo or Luganda). All documents were translated into local languages from the English versions twice, independently, by two researchers. Each of these versions was translated back to English by a third researcher, with any discrepancies discussed amongst the group and an agreed translation decided. This is the best practice method for translation(327, 328). Full instruments are in Appendix A.

The APCA African POS

The development, validation and properties of the POS are described inSection B.5.iv. The POS is applicable to people with cancer or HIV in Africa (255) and its ten items address the primary physical, emotional and spiritual concerns of patients and families. Seven are addressed to the patient and three to the carer. They include questions relating to the four dimensions of palliative care: physical (pain, symptoms), psychological (worry, sharing feelings), spiritual (peace, feeling life worthwhile) and social (help and advice for family).

The ECOG

The Eastern Co-operative Oncology Group is a clinician-rated single item measure of performance, the most widely used performance measure in clinical research

(329), also administered at all four time points(330). Scores range from 0 (normal activity) to 4 (unable to get out of bed).

Demography

Basic demographic and medical details were collected using a brief questionnaire administered at T0 (recruitment to study). Four pieces of clinical information were collected at T1: World Health Organisation (WHO) stage, date and result of most recent CD4 test if the participant had one, and date of ART initiation, if used. These questions were moved from T0 to T1 because in piloting HCWs pointed out that the information would not be available to new participants at T0. The demography questionnaire also included the DHS Wealth Index questions, widely used to create a measure of relative wealth(331).

E.2.vi Ethical approval and data storage

The study design was approved by the Research Ethics Committee of King's College London (Ref CREC/06/07-140), the Ethical Review Committee of Kenya Medical Research Institute (KEMRI/RES/7/3/1) and the Uganda National Council for Science and Technology (UNCST, Ref SS 1964). Twice during the study, changes were made to the protocol and these were also approved by each committee. Ethical approval documentation is included in Appendix B.

During data collection all questionnaires were stored separately from consent forms, in a locked filing cabinet at the facility. Upon study completion, anonymised questionnaires were taken from the facility to the APCA offices for storage in locked filing cabinets until 2015. These arrangements were in line with ethical requirements and the UK Data Protection Act 1998.

E.2.vii Data collection and management

Six research assistants in Kenya and Uganda were each responsible for two facilities, and supported by a research manager. They trained health care workers

at the facilities to collect and manage data. The research workers themselves were trained by KCL staff including myself in a five-day programme with a pilot.

Health workers at the twelve facilities recruited participants, obtained their consent, and recorded their answers to the questionnaires, with follow-up appointments at monthly intervals for three months. These were referred to as T0 (baseline), T1, T2 and T3.

Data collection took place between January and September 2008, with recruitment to the longitudinal quantitative study terminating in June. With the exception of CD4 counts, data for the longitudinal study were self-reported by the participants. HCWs recruited patients and collected data in the course of their regular duties. Funding was provided to the facility directors to support data collection, including purchase of a computer. APCA staff trained HCWs to take informed consent and complete questionnaires. A researcher maintained contact with each facility through regular visits to observe data collection, check the use of appointment diaries and regular data entry, and deliver additional training as necessary.

Research assistants were monitored through conference calls with KCL every fortnight. On the calls, researchers reported data collection progress at each site and raised any problems or concerns. A field manager based in Uganda was in constant email contact with the KCL team. KCL produced three issues of a study newsletter which were circulated to research assistants and participating facilities every two months to build unity and involvement with the project.

Early in data collection it became apparent that participants could not always remember the date and result of their last CD4 count. Less than 50% of participants were able to provide a CD4 count and it appeared that these were biased towards people who were more ill or concerned about their health. Accordingly, permission was granted by the three ethics committees overseeing the study to search patients' records for CD4 counts. Researchers visited each facility after the cohort was completed, and copied CD4 counts for the study participants into a specially designed form which preserved anonymity while linking records to participants. CD4 count was the only piece of information obtained in this way.

E.2.viii Data entry and validation

Immediately after collection, data were entered into a pre-designed EpiData v3.1 database with conditional checks for internal consistency, by a trained administrative staff member. When participants had exited the study, patient packs were transferred to the APCA offices where research staff conducted a second round of data entry and validation. Discrepancies were corrected by manual referral to questionnaires, and results were revalidated until the two datasets were identical. The CD4 information from patient records was entered into a separate EpiData database and merged into the main dataset, which was exported to Stata 10.0 for analysis.

E.3 Analysis questions

Each of the four objectives is achieved by answering one to three research questions, as shown below.

Objective 1: In adults with HIV in Kenya and Uganda, to determine prevalence and severity of palliative care-related problems within two weeks of diagnosis

1a: What are the demographic characteristics of the sample of people newly diagnosed with HIV in Kenya and Uganda?
1b: What are their scores in the seven patient-completed items of the POS?
1c: What are their total POS scores?

Objective 2: To investigate whether demographic variables or CD4 count are associated with prevalence and severity of palliative care-related problems at diagnosis

2: At T0, is severity of POS item problems associated with age, gender, CD4 count, socioeconomic status, country, physical function or education?

Objective 3: To determine change in palliative care-related problem severity over a three month period

3a: Do POS scores change over a three-month period, and if so do they change from one month to the next?
3b: Does total POS score change over a three-month period?

Objective 4: To investigate whether demographic variables or ART use are associated with change in palliative care-related problem prevalence over time

4: Is any change in prevalence of moderate/severe POS item problems over time associated with age, gender, socio-economic status, education or receipt of ART during follow-up?

E.4 Analysis plan

E.4.i Introduction

Table E-1 below presents the analysis plan. It consists of four parts, each part corresponding to one objective.

E.4.ii Definitions of variables in the analysis plan

Dependent variables

The POS was selected as the outcome measure because the aim is to identify palliative care problems at diagnosis, rather than more general health-related QoL. The POS is directed at palliative care problems and is responsive to change over time. It has been validated in Uganda and South Africa, showing good psychometric properties and face validity (256). It consists of ten items, seven completed by the patient and three to the carer. Each item has a Likert scale of six responses numbered 0-5. The carer items were not analysed, because only a small and unrepresentative number of patients (16%) were accompanied by a carer.

In the questionnaire, not all POS items are scored in the same direction. In some cases 0 is the worst end of the scale and in others it is the best, in order to reduce the risk of participants habitually giving the same answer each time. For analysis the fourth, fifth, sixth and seventh POS items are recoded to reverse the response order, so that for all items 0 represents the best situation (no problem) and 5 represents the worst.

The POS is designed to be multidimensional and has a low Cronbach's alpha of 0.6, indicating that it does not measure a single construct(256). In general terms this makes it unsuitable for combination into a single outcome measure. However,

Table E-1: analysis plan

Part	*Research question*	*Dependent variables*	*Independent variables*	*Analysis*
A	**1a**. What are the demographic characteristics of the sample of people newly diagnosed with HIV in Kenya and Uganda?	Gender, age categories, education level, country Time from diagnosis to T0 Socio-economic variables		Mean, standard deviation, percentages Principal-components factor analysis
	1b. What are their scores in the seven patient-completed items of the POS? **1c.** What are their total POS scores?	POS scores at T0 (coded 0,1,2,3,4,5) Addition of the 7 POS item scores (0 to 35)		Percentages Percentages
B	**2**. At T0, is the severity of POS item problems associated with age, gender, CD4 count, socio-economic status, country, physical function or education?	POS scores at T0, coded ternary (0/1=none/mild 2/3=moderate 4/5=severe)	Presence of CD4 result Gender, age, education, wealth quintile, country Physical function CD4 count	<u>Bivariate</u> Chi squared tests Non-parametric score tests for trend <u>Multivariate</u> Stratum-specific odds ratios (ORs) Ordinal logistic regression Likelihood ratio tests
C	**3a**. Do POS scores change over a three-month period, and if so do they change from one month to the next?	POS scores at M0, M1, M2 and M3 (coded 0,1,2,3,4,5)		Proportion of net change and 95% CI
	3b. Does total POS score change over a three-month period?	Addition of the 7 POS item scores (0 to 35) at M0-M3		Analysis of variance
D	**4**. Is any change in prevalence of moderate/severe POS item problems over time associated with age, gender, socio-economic status, country, education or receipt of ART?	All POS scores, coded binary (0/1=none/mild 2/3/4/5=moderate/severe)	Gender, age categories, education level, wealth quintiles, physical function ECOG at all time points ART use at all time points	<u>Bivariate</u> Fixed-effects conditional logistic regression <u>Multivariate</u> Multivariate fixed-effects conditional logistic regression

a unified score is useful to indicate whether some individuals have multiple and complex problems. Total POS score was calculated in the simplest way possible, by summing the seven outcome scores to create a single variable scored from 0 (no problems in any area) to 35 (overwhelming problems in all areas).

For Part A and Part C of the analysis, the complete POS six-point scale is used as the outcome, but the statistical techniques used to examine the association of POS scores with independent variables do not allow for a six-point outcome scale. In Part B, the scale is reduced to a ternary (three-point) score; 0 and 1 are coded ‘no/mild problem’, 2 and 3 ‘moderate problem’, and 4 and 5 ‘severe problem’. For the multivariate fixed-effects logistic regression in Part D a binary outcome is used, with 0 and 1 coded ‘no/mild problem’, and 2, 3, 4 and 5 coded ‘moderate/severe problem’.

Independent variables

Gender: a dichotomous variable, male (0) and female (1).

Age: year of age was recorded as a continuous variable. For analysis it is coded into an ordinal variable with the three groups 18-25, 26-40, and 41-59 (the maximum). The reason for these groupings was to divide the population based on their experience of HIV. People aged over 40 in 2008 were at minimum 16 years old when HIV was recognised in Uganda, in 1984. The 26-40 year olds were children and the 18-25 year olds had not yet been born. The theory was that these different perspectives on HIV might influence reaction to diagnosis and perception of stigma.

Level of formal education: recorded in five categories (none, primary, secondary, diploma and degree). For analysis the diploma and degree groups are combined due to their small size. The group with no formal education was small (19 at recruitment) but it was kept separate, because complete lack of education is closely associated with non-literacy which is a barrier to health care.

Country: A binary variable created from the facility ID number. Kenya is the baseline (coded 0) and the variable ‘country’ in models indicates the comparison of Uganda (coded 1) with Kenya.

Physical function: the ECOG records physical function on a scale from 0 (fully active) to 4 (completely disabled). In analysis response 1 is coded ‘best physical function, 2 as ‘middle physical function’, and the responses 2, 3 and 4 are combined into one group, ‘worst physical function’, due to the small number of participants (n=30).

Disease progression: WHO stage, most recent CD4 count and date of the CD4 count were recorded at T1. These details were completed at T1 rather than T0 to maximise completion, as some participants might not have received their CD4 results at the time of completing T0. It was anticipated that most CD4 tests would be completed within a few days after registration and recruitment.

ART use: Use of ART was recorded each month as a binary variable. Among non-recipients of ART, it was not possible to distinguish patients who were not eligible from those who would have benefited from ART but did not have access to it. All facilities in the study offered ART. Details of AIDS-defining illnesses are unknown and CD4 counts are not available for all participants.

Wealth Index quintile

The DHS Wealth Index was developed by MEASURE DHS in collaboration with ORC Macro for use in demographic health surveys worldwide(331). The method has been widely used in over 44 countries in and beyond Africa(332). It uses an assets-oriented approach to determine relative household wealth within a population. In the standard Wealth Index questionnaire, the assets are ownership of goods (mobile phone, radio etc), house construction materials, fuel use, drinking water and sanitation. The responses to these variables are subjected to principal-components factor analysis to create a continuous score, which is divided into quintiles to represent relative socioeconomic level for analysis.

The reason for using assets rather than a more straightforward measure of expenditure or income to determine wealth status is that in a low-income setting a considerable proportion of exchange may not be cash based, and so estimates of payment or cash expenditure will be unreliable(331). In many developing countries the majority of work is subsistence farming, and payment for services is made in kind. Wealth is also thought to have a lower volatility than either income or expenditure. Income may be related to time of year, particularly to harvest, while expenditure may be much higher at weddings or festivals. The Wealth Index has been validated against more complex measures of poverty in India and Nepal and performed well(333).

Wealth is considered to be an unobserved latent variable underlying the possession of assets. As with other latent variables such as quality of life, principal components analysis is used to create a single index. The index is based on relative wealth because it has been shown that relative wealth is more closely associated with health status than absolute wealth. A further advantage of this approach is that it provides information directly relevant to the question of interest, i.e. the health status of the poor compared to the better-off. For the same reason, the index is divided into categories (traditionally but not necessarily quintiles) so that the effects of poverty can be observed within a group(331). The quintiles are termed ‘lowest’, ‘second’, ‘middle’, ‘fourth’ and ‘highest’, coded 1-5, with the lowest group used as the reference in this analysis.

The Wealth Index variables were included in the demographic questionnaire administered at recruitment (Appendix A). They are:

- Material used to make the walls, roof and floor of the house
- Type of toilet
- Main source of drinking water
- Fuel used for cooking
- Household ownership of car, bicycle, refrigerator, television, mobile phone and radio

E.4.iii Missing data

Some participants were lost to follow-up(LTFU) without return, while others missed certain appointments and later returned. The number and proportion (as a percentage of those recruited) to complete interviews at each time point is displayed in a flowchart, showing reasons for LTFU where known. The number of participants to complete one, two, three and four interviews is calculated and presented in a second flowchart. The number of newly diagnosed participants interviewed at each time point is tabulated by facility.

Missing data are categorised as either missing completely at random (MCAR), missing at random (MAR) or missing not at random (MNAR). MCAR means that no other observations are associated with the probability of missingness. Data are MAR when missingness is associated with other covariate, and MNAR when missingness is associated with the value of the missing data(334). These definitions are of great theoretical importance, but limited practical use. By definition it is impossible to know whether data are MNAR because this depends on the unobservable values. MCAR is a relatively rare situation in health research where missingness is usually associated with illness burden to some degree.

Data can be also missing in two ways, either from a missing item in a questionnaire (item non-response) or from the absence of the entire questionnaire (unit non-response)(335).

1. Item non-response

Item non-response occurs if participants do not wish or are not able to answer certain questions and if there are no consequences to leaving them blank. Item non-response would have been a problem in this study because the MOS-HIV summary scores can only be completed if all 35 items are present. Therefore the study design included several mechanisms to improve item response. The questionnaires were completed by trained health care workers, with monitoring for completion by research assistants every two weeks, and the database into which they were entered included a consistency check for missingness which was

reported back to the study managers every two weeks. Item non-response is expected to be very low for all variables, with the exception of CD4 count, the only piece of information collected from patient records.

Having a CD4 count will be used as a dichotomous outcome variable to test whether it is associated with other variables (MAR) or not (MCAR). It is not possible to test whether data are MNAR.

2. Unit non-response

Unit non-response occurs when an appointment is missed or a questionnaire is not returned. In this study it occurred when participants either attended the facility and did not wish (or were not able) to participate in the study, or they did not attend the facility. There were no resources for follow-up of patients who did not attend, other than those used by the facilities themselves for patient care.

There are many types of imputation but they fall into two main forms, being based either on previous data or on previous trajectories. The simplest form of imputation based on previous data is last observation carried forward (LOCF), which repeats the last known value in all subsequent data points. Alternatives include replacing missing data with the mean of all previous data points(335). The assumption is that variation between individuals is greater than variation over time, such that variation within an individual and over time can be ignored. This assumption is not appropriate for my dataset in which outcomes are expected to vary within individuals over time. The second form of imputation extends an observed trajectory and imputes unobserved data from it. Examples include linear regression, Markov chain, and conditional probability imputation(335). This is a better option because data are allowed to vary over time, but it artificially constricts the variability of data.

Multiple imputation is increasingly preferred(336). It simply repeats a selected imputation technique between three and ten times, and combines the results of data analysis in each of these newly generated datasets. In this way, the variability within a dataset is maintained, but any faults in the original choice of imputation

method remain. All imputation techniques overinflate observed effects(335). Patterns within the observed data are magnified and standard errors are reduced, even though no new information has been added. Any imputation technique makes certain assumptions about the data(336). Similarly, the choice not to use imputation makes an assumption about the data, namely that the section which is missing is not different from that which is observed.

The analysis plan has four distinct parts, each using a different version of the dataset. Parts A and B are cross-sectional at baseline, and so unit non-response is not an issue because the sample was complete at baseline. The approach to missing data is discussed in the methods of Parts C and D, which use longitudinal analysis.

E.4.iv Part A: Participant characteristics

The first objective is to determine prevalence and severity of palliative care-related problems within two weeks of diagnosis. Two analysis questions are linked to this objective and the first is

1a:What are the demographic characteristics of the sample of people newly diagnosed with HIV in Kenya and Uganda?

Demographic characteristics of participants are described. The number of days from diagnosis to recruitment is displayed in a bar chart and the mode is calculated. Socioeconomic variables are recategorised as shown in Table E-2, and the number and percentage to report each category are presented in a table.

The recategorised DHS Wealth Index variables from the demography questionnaire are incorporated into a principal components factor analysis (PCA) to generate a single relative Wealth Index, which is split into five ordinal quintiles of equal size following the method used in the Demographic Health Surveys(331, 332). Socio-economic variables are presented by wealth quintile in a table, to portray the characteristics of participants at each level of relative wealth. The

loading of each variable onto the wealth factor in the PCA is presented in Appendix D.

Participants from the two study countries, Kenya and Uganda, are compared to establish whether they can be analysed as a single group or whether there are systemic differences between the two. A table is populated with the following information, calculated for each country separately:

- Proportion of females as a percentage
- Mean and standard deviation of age
- Percentage reporting each of the recalculated education categories in Table E-2
- Median and inter-quartile range of number of days from HIV diagnosis to recruitment
- Proportion with a recorded CD4 count, expressed as a percentage
- Median and IQR of CD4 count for those who have one
- Proportion within each of the previously calculated wealth quintiles, expressed as a percentage

Tests for significant difference are conducted as follows: difference between Kenya and Uganda in terms of binary variables (gender and having a CD4 count) is analysed using chi-square tests. Ordinal variables (education level, grouped number of days since diagnosis, and wealth quintile) are compared using analysis of variance (ANOVA). Continuous variables (age and CD4 count) are compared using t-tests. In all cases the level of significance is 5%.

Table E-2: recategorisation of socioeconomic variables for factor analysis

Variable	Questionnaire values	Analysis values
Highest level of schooling attended	None	None
	Began primary	Began primary
	Began secondary	Began secondary
	Diploma	Diploma or higher
	Degree	
Material used to make walls of house	Thatched/straw	Thatch/mud and poles
	Mud and poles	
	Unburnt bricks	Unburnt bricks
	Burnt bricks with mud	Burnt bricks with mud
	Metal sheet	Metal sheet/cement block
	Cement blocks	
	Stone	Stone/wood/burnt bricks
	Wood/timber	
	Burnt bricks with cement	
Material used for roof of house	Thatched	Natural
	Wood/planks	
	Corrugated iron sheets	Corrugated iron sheet
	Asbestos	Finished
	Tiles	
	Tin	
	Cement/concrete	
Material used for floor of house	Earth, mud, sand	Earth
	Cement	Cement
	Linoleum	Other finished
	Parquet/polished wood	
	Tile	
	Carpet	
	Stone	
Source of drinking water	Bottled	Bottled/piped inside house
	Piped inside house	
	Piped outside house	Piped outside house
	Protected well	Other safe
	Borehole	
	Spring/rain water	Other unsafe
	Unprotected well	
	River/stream/pond	
	Tanker truck	
Fuel source	Electricity	Electricity/gas
	LPG/natural gas	
	Biogas	
	Paraffin/kerosene	Paraffin/coal
	Coal/lignite	
	Charcoal from wood	Charcoal
	Firewood	Firewood/straw/dung
	Straw/grass	
	Dung	

E.4.v Part A: Univariate analysis of problems at baseline

The second analysis question for the first objective is

1b: What are the scores of people newly diagnosed with HIV in the seven patient-completed items of the POS?

The percentage of participants to report each response category on each POS item is calculated and presented in a table. For one item (having enough help and advice for the family to cope), subgroup analysis is performed on participants who were diagnosed more than three days prior to recruitment, to avoid the bias that participants could report little help or advice in the past three days if they had not known they were HIV positive. Stacked column charts are plotted to show the distribution of each POS item score.

The third analysis question is

1c: what is the total POS score of people newly diagnosed with HIV?

To answer this, the seven patient-completed POS item scores are added together to create a total POS score, and the distribution at T0 is plotted as a histogram. The distribution is reported in percentage categories (0-4, 5-9, 10-14, 15-19, 20-24, 30-35).

E.4.vi Part B: Multivariate analysis of problems at baseline

The second objective is to investigate whether demographic variables or CD4 count are associated with prevalence and severity of palliative care-related problems at diagnosis. The research question is:

2: At T0, is the severity of POS item problems associated with age, gender, CD4 count, socio-economic status, country, physical function or education?

The seven outcome variables each have six possible scores. To reduce the number of tests and hence the risk of Type II error, the scores are converted to

three categories, called ‘low/none’ (0 and 1), ‘medium’ (2 and 3) and ‘severe’ (4 and 5). When recoded into three response levels, the POS item scores are referred to as ternary item scores.

Not all participants have a CD4 count. Before using the CD4 results in analysis, presence of a CD4 count is tabulated against ternary POS item scores, with chi squared tests to check for confounding. If the existence of a CD4 test result is associated with outcomes, the CD4 results cannot be analysed against outcomes.

The analysis plan, repeated for each of the seven outcome variables, is as follows:

1. Bivariate analysis

Values of the seven independent variables (gender, age, education, wealth quintile, physical function, country and CD4 count) are tabulated against the ternary dependent variable. The definitions of these variables are described in Section E.4.ii. Five of them do not vary over time; for physical function, the value at baseline is used, and for Cd4 count only the baseline value is used because very few participants (15.5%) have more than one recorded CD4 count.. Chi squared tests are performed to identify variables which may be associated with the outcome. Additionally, for the five ordinal variables (age, wealth quintile, education level, CD4 count and physical function), a non-parametric score test for trend is performed. A test for trend makes more efficient use of the data than a chi squared test, which is only able to detect unlikely deviations from the expected distribution of two completely unrelated variables. Any real association between age, wealth, education or physical function and an outcome is expected to show a dose-response relationship. A test for trend is more likely to detect such a relationship, which may not register as significant on a chi squared test. However, a distribution which deviates from the flat in more than one direction (for example, a higher than average association for people of middle income), which might be caused by chance, is more likely to have a low p-value on a chi squared test than a test for trend. Both are useful, but in case of conflict the test for trend is more appropriate.

A chi squared test assumes a large sample of random, unrelated observations, with a minimum of five observations per cell. Both independent and dependent variables have been recoded to reduce the number of cells and increase cell size

in order to lessen the risk of Type II error, but some small cells remain. The usual recourse in this case is to use Fisher's exact test, which is more accurate in the case of very unbalanced tables or when cells are small.

The algorithm for deciding whether to use Fisher's exact test is derived from Kirkwood and Sterne(337) and is as follows:

- For 2x2 tables, if N (the total sample) is greater than 40, the chi^2 test is always valid.
- For larger tables, chi^2 is valid if
    - The expected value is greater than 1 for all cells, and
    - The expected value is greater than 5 for at least 80% of cells

The expected value (E) of a cell is the total of the row multiplied by the total of the column and divided by N. When chi^2 is not valid, Fisher's exact test will be used.

Independent variables that have a less than 10% probability of forming such a distribution without a true association will be considered for possible confounding and then taken forward into multivariate analysis. This is a higher probability than the normal 5%, to reduce the risk of eliminating variables too early.

2. Multivariate analysis

The main technique used in the multivariate analysis is an extension of logistic regression, which allows an ordinal outcome to be used instead of the usual binary one. Hence it is called ordinal logistic regression (OLR). The outcomes are ternary, with three values (low, medium and high). The outcome can be analysed in two ways. Either separate odds ratios are produced for the odds of medium problems to low and high problems compared to low, or a single combined odds ratio is produced giving the average odds of medium versus low and high versus medium. The first method treats odds of medium problems and high problems as completely distinct, as though the outcome was a categorical variable. The second method assumes a consistent relationship between covariates and the odds of increased problems, treating the outcome as a true directional ordinal variable. The first model is more sensitive, but the second uses fewer terms and is more robust.

In this analysis, the first method is used initially. This requires the creation of indicator or dummy variables to represent the options ‘medium problems’ and ‘high problems’. If the outcome is directional, then the OR for high problems should be around double the OR for medium problems. If this is the case, then the second method is used to fit an ordinal model, and the two are compared using a log likelihood test. The categorical model will only be retained if the test proves that it is significantly better than the ordinal model. The ordinal model, being simpler, is preferable in the absence of a significant difference between the two.

Possible confounding and interaction between independent variables is investigated using stratum-specific odds ratios (ORs), which are calculated using OLR. It is not possible to calculated an adjusted OR using an ordinal outcome (there is no equivalent of a Mantel-Haenszel test). This makes it more difficult to interpret whether confounding is present, so a judgement must be made based on feasibility, the unadjusted and stratum-specific ORs, and tabulation of the two independent variables. Variables which are accepted as associated with the outcome are taken forward into multivariate OLR.

First, independent variables are imputed as non-ordered categorical, using indicator variables for each value. Where the stratum-specific ORs indicate possible effect modification, an interaction term is added to the model. Next, several approaches are tried to simplify the initial model, to improve efficiency without loss of effectiveness. The interaction term is removed if it seems unnecessary (Wald test result shows no significance). Independent variables are imputed as ordinal if the log ORs for each response are similar, linear, and do not cross zero. At each stage the likelihood test statistic is calculated and a likelihood ratio test is used to determine whether the new model is significantly different from the previous one. The final model is presented using log odds ratios (Box 1) and interpreted.

Box 1: Why report log odds ratios?

Table E-3 is a dummy table showing the information presented from an OLR model. The output is explained below.

Table E-3: dummy table to show association of independent variables with ternary POS score using OLR

	Log OR	SE	Z	P	OR	95% CI of OR
Independent variable 1						
Independent variable 2						

Logs are used because a log odds distribution can conform to a Normal distribution and be used to derive a z statistic. The second column of the table gives the overall adjusted ratio between log odds of the outcome at one level and the next (i.e. the combined log odds of severe problems compared to moderate, and moderate compared to mild/none). The next column gives the standard error of the log OR. The coefficient divided by the standard error gives the z statistic, which follows a parametric distribution and is used in a Wald test to test the null hypothesis that the log OR is 0, i.e that the odds of the outcome are the same in both groups. A comparison of the z statistic with a Normal distribution obtains the p-value. In this analysis, the null hypothesis is rejected when p is less than 0.05. This indicates the observed OR is so far from 1 that it would have a lower than 5% probability of occurring by chance.

The OR is derived by finding the exponential of the log term, and is presented with its 95% confidence intervals in the last two columns of the table. The important point is that the OR is the easiest result to interpret, but the statistical test is actually carried out on the log OR. For this reason, log ORs are presented to three decimal places but ORs to only two.

E.4.vii Part C: Univariate analysis of problems over time

The third objective is to determine change in palliative care related problem severity longitudinally in a three month period. It has two research questions:

3a. Do POS scores change over a three-month period, and if so do they change from one month to the next?

3b: Does total POS score change over a three-month period?

To answer both of these questions, the number of days between observations is recoded into a variable for month, as described below.

1. Time intervals

The protocol specified that interviews should ideally take place at one-month intervals but that if participants were not able to return on the specified day, an interview up to seven days before or after was acceptable. In other cases, the time between interviews was not constant because participants missed one appointment and returned two months later.

The variation in length between interviews was thus not entirely standard, which could be a cause of bias. For the PEPFAR PHE, it was reasoned that change in outcome would probably be more affected by the number of contacts with health services than the passage of time. In the PHE, the time T0 has no particular meaning. It indicates either a new diagnosis or a new presenting problem of any kind. Therefore the time elapsed since T0 is not a variable in itself, and the fact that the time between T0 and T1 is not fixed is not a problem.

For the newly diagnosed group, the situation is different, as T0 represents a point in time within 14 days after diagnosis with HIV. The passage of time since diagnosis may be associated with change in outcomes independently of care and support received during that time, so time must be consistently measured. To achieve this, data points are recoded M0, M1, M2 and M3 (for Month), rather than the original T0, T1 etc. T0 and M0 are always the same. All M1 observations take place 30 days after M0 (the average length of a month in the data collection

period), plus or minus seven days. Observations earlier or later than this are rejected. The definition of new diagnosis accepted data collection up to 14 days after diagnosis, and it was consistent to continue to use 14-day periods of time.

This approach involves recoding some data points, so that for example a data point marked T2 but collected 85 days after recruitment is recorded M3. Interviews completed four months after T0 are coded M4, and so on. A table is populated with the number of interviews to take place in each month. A disadvantage is that some data points are lost.

2. Analysis plan

The first research question involves measurement of change in POS item scores over time in the absence of any covariate. The null hypothesis is that POS scores do not change over time. For any two time points, proportion of net change is defined as the percentage of individuals whose scores reduce (i.e. get better) between the first time point and the second, minus the percentage whose scores increase(338). Although the underlying data are non-parametric, the change value is modelled as parametric and has a standard error from which a 95% confidence interval can be calculated. Change is very robust to parametric assumptions(338).

The proportion of net change test is better for showing change than a Wilcoxon matched pairs signed-rank test. A Wilcoxon test assigns ranks before comparison of the two variables, allowing completely different paired measures to be compared. The process causes the absolute difference between points to be lost(338). Furthermore, a Wilcoxon z-test does not indicate direction of change, only that the two populations are not identical.

The other advantage of a proportion of net change test is that it can be conducted using only spreadsheet software such as Microsoft Excel, or even by hand, and the principles involved are no more complicated than the concept of standard error and 95% confidence intervals. The development of an evidence base for palliative care in Africa is hindered by lack of research funding, capacity and skills(242). An

example of a simple, replicable, appropriate and readily interpretable method for longitudinal analysis could help researchers in Africa to build an evidence base, using the data they already have in the form of patients charts and routinely collected information.

For each POS item, the method is

1) Graph score distributions using stacked bar charts for the time points M0 to M3
2) Calculate the difference between POS item score at M0 and M3 (M3 score minus M0 score), for all participants who completed interviews at both times
3) Calculate the proportion of participants to register each possible value of change, from -5 to 5, and display these in a table
4) Sum the percentages to calculate the proportion whose score decreased
5) Sum the percentages to calculate the proportion whose score increased
6) Subtract the proportion whose score increased from the proportion whose score decreased to derive the proportion of net change
7) Calculate the standard error of the proportion of net change using the usual formula and use it to obtain 95% confidence intervals

If the 95% confidence intervals of the proportion of net change do not cross or include zero, then the null hypothesis is rejected and the variable is deemed to change over time.

Following this, the proportion of net change is also calculated for the time periods M0 to M1, M1 to M2 and M2 to M3 to establish whether change is steady or punctuated. This is only done if the first test demonstrates change over the entire time period, as testing series of time points against each other amounts to subgroup analysis. This means that a short-term, unsustained improvement is not detected, which is acceptable, because in this population such an effect would not have worthwhile benefit. In a population near the end of life, short-term improvement could be more valuable.

The second research question for Part C is

3b: Does total POS score change over a three-month period?

Total POS score is calculated as described for Part A, at each time point M0, M1, M2 and M3. Mean and standard deviation are presented, and total POS score is compared over the four months using analysis of variance.

3. Missing data

Available case analysis was used for this objective. The proportion of net change technique has individual-level change by paired analysis as its outcome and any imputation process would alter this result, either reducing it by using imputation based on prior observations, or increasing it by using imputation based on prior trajectory. Available case analysis incorporates known assumptions, rather than introducing the unknown assumptions of adding to observed data. Furthermore, proportion of net change is designed to be a simple technique that does not require advanced software or statistical training, both of which are lacking in Africa. The stacked bar charts provide a useful mean to represent the effect of missing data as they plot actual numbers of participants rather than percentages.

E.4.viii Part D: Multivariate analysis of problems over time

The fourth and last objective is to investigate whether demographic variables or ARV use are associated with change in palliative care-related problem prevalence over time. It has one analysis question:

4: Is any change in prevalence of moderate/severe POS item problems over time associated with age, gender, socio-economic status, country, physical function, education or receipt of ART?

The longitudinal extension of multinomial logistic regression can be used to analyse the effect of covariates on an ordinal outcome over time.

While traditional techniques require repeated observations at equal distances for all participants, represented by the use of monthly intervals in Part C, longitudinal analysis can be fitted to a continuous time variable with non-standard observations

(Box 2). The Stata command *xtset* is used to define the dataset as a cohort with repeated observations unequally spaced over time. For each observation, the number of days since recruitment (T0) is calculated, and this number of days is used as the time variable.

The number of days from T0 to the date of data collection is expected to follow a left-censored Poisson distribution, with a long tail to the right. To prevent outlier bias, the mean and standard deviation of the time variable are calculated and observations more than three standard deviations beyond the mean are rejected.

The six independent variables used previously (age, gender, wealth quintile, education level, country, and physical function) are included, plus one other: use of ART, a dichotomous variable. Physical function and ART use have the additional property that they are time-varying, recorded at each interview. The seven dependent variables are analysed as dichotomous, divided into no/low problem, coded 0, and moderate/severe problem, coded 1. The longitudinal extension of logistic regression is applied.

This coding groups all scores from two to five into a single undifferentiated outcome, which reduces sensitivity to degree of problems. In this case the loss of detail was accepted because all problems were considered to imply a possible need, and to be amenable to possible alleviation. The sample population is of relatively well adults with a high expectation of good quality of life.

Box 2: What is longitudinal analysis?

Longitudinal analysis was developed from multi-level modelling in education, to take account of the clustering effect of pupils within classes and classes within schools. Repeated observations of the same individual at different points in time can be considered as a cluster, with the added element of direction. Longitudinal analysis methods can also be applied to binary outcomes, as used here(339).

There are two approaches to longitudinal analysis. The first is to conduct cluster-specific analysis and record the extent of variation between clusters. In this case, remembering that a cluster equals an individual, ordinal regression would be conducted for the association between covariates and outcome over time for each person in the sample, using the same equation for everyone but allowing the intercept and/or the slope to vary between individuals(340). The extent of this variation forms part of the outcome. The other approach is to use a generalised equation which estimates the average association between covariate and outcome over time for the entire sample. Most of the time the two methods give similar results, but they are based on different underlying principles(341). I chose the second approach, which when applied to logistic regression is known as the population-averaged approach. The cluster-specific approach is more appropriate when hypotheses are being tested or when the real odds of a given outcome are required. The population-averaged approach, as the name implies, analyses at a population level rather than an individual level. Its output is interpreted as the average odds of any given individual having the outcome. Given that so little information exists regarding palliative care-related problems at HIV diagnosis, it is more relevant at this point to seek general trends which can inform further research and care. Furthermore, the population-averaged approach in most cases produces odds ratios which are slightly closer to 1, so it is more conservative(338).

For each of the seven POS items, the method is as follows:

1. Create a dichotomous outcome measure, coding no/mild problem as 0 and moderate/severe problem as 1
2. Fit a population-averaged logistic regression model predicting the odds of moderate/severe problem adjusting for time in days since T0
3. Repeat step 3, adding one extra covariate:, in turn, gender, age, wealth quintile, education, country, physical function, and ART use
4. Identify independent variables associated with the outcome with a p-value of less than 0.25 in steps 3 and 4 above, and include them in a multivariate population-averaged conditional logistic regression model with significance set at 0.05
5. If any covariate is not significantly associated with the outcome, remove the covariate with the highest p-value and refit the model. Repeat stepwise until all remaining covariates are significantly associated with the outcome
6. Obtain predicted values from this model
7. Plot the predicted population-averaged values over time and display the graphs

1. Missing data

Cross-sectional time series logit analysis is a special case of a generalised estimating equation(GEE). Specifically, it is a GEE model with a binomial distribution of the dependant variable, a logit link function and an exchangeable correlation structure. When data are MCAR, GEE analysis is unaffected. Additionally, GEE methods have been shown to maximise efficient use of available data, with low sensitivity to data MAR. A paper using an experimental dataset with GEE found that analysis of observed data was comparable with several imputation methods and avoided the problem of underestimated standard errors which is common to all imputation(334). I opted for the most conservative approach, which in this case was available case analysis of observed data without imputation, since there was evidence imputation had little effect on results other than exaggerating the precision of standard errors. Change over time was the outcome and any observed change would only be inflated by imputation.

F Results

F.1 Overview

This chapter presents the results in four parts, each designed to fulfil one objective. Part A consists of descriptive cross-sectional analysis at baseline (within two weeks after HIV diagnosis). Part B compares prevalence and severity of problems at baseline by demographic and clinical characteristics. Part C displays POS scores at monthly intervals and measures the change between them. Part D is a more complex analysis of change over time, using all observations, and adjusting for the effect of demographic and clinical variables. Table F-1 below shows the four parts and their attributes. Part A includes neither time nor other covariates; B and D include other covariates; C and D include time.

Table F-1: overview of results

		Effect of time
	Part A	**Part C**
Effect of covariates	**Part B**	**Part D**

F.2 Recruitment and retention of participants

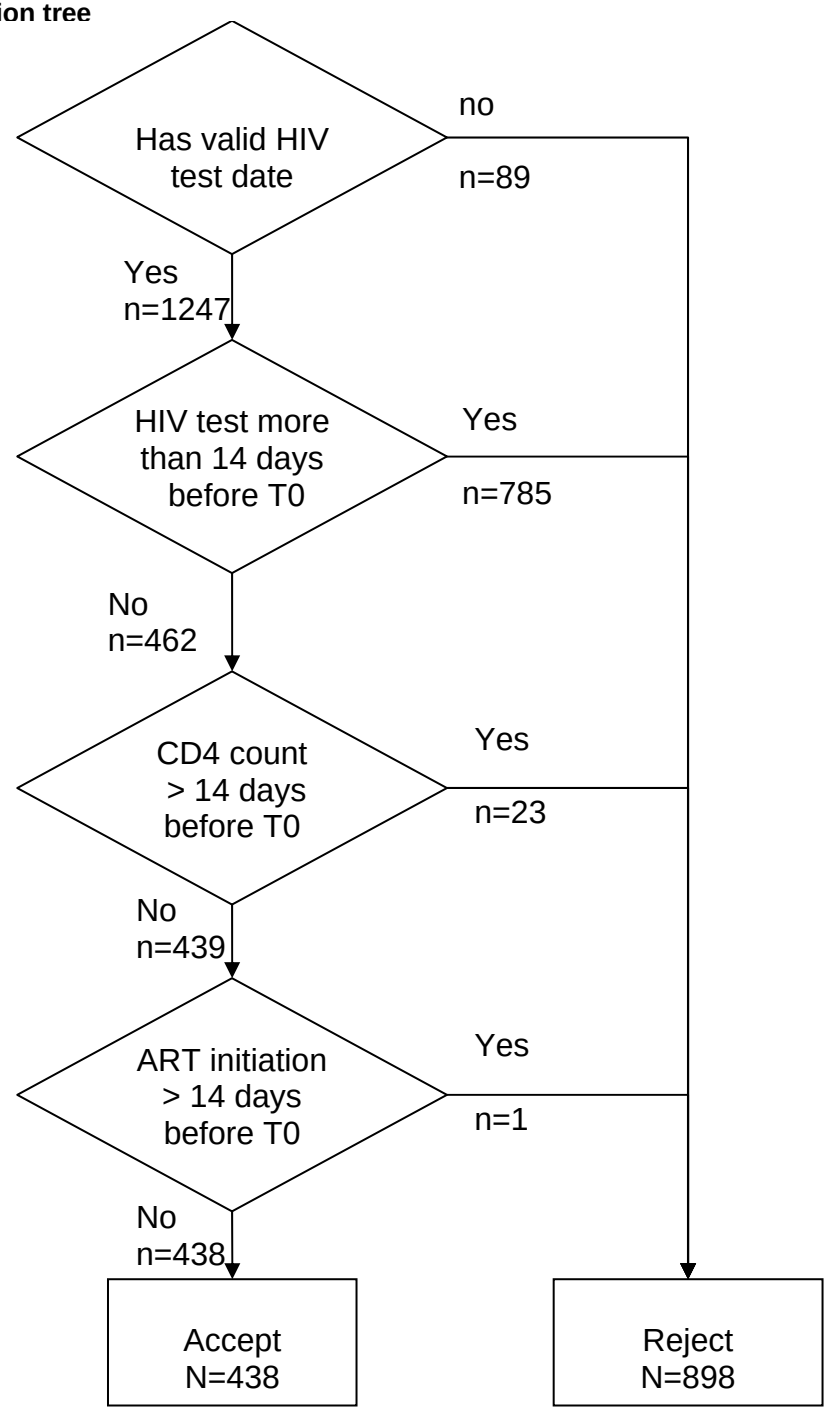
In Kenya, of the 696 people approached, 641 gave a valid date of their HIV test, and 266 of the HIV test dates (41.5%) fell on the day of recruitment or up to 14 days previously. Of those 266, 18 were rejected because their records showed a CD4 test had been performed more than 14 days before T0, and one more was rejected because ART initiation preceded the 14 day limit. This left 247 newly diagnosed participants from the Kenya cohort.

In Uganda, the 640 potential participants included 606 with a valid HIV test date, and 196 (32.3% of those with a date) reported being diagnosed HIV positive within 14 days prior to T0. Five were excluded because they had a CD4 count predating this time, leaving 191. The 191 from Uganda added to the 247 from Kenya gave a total of 438 newly diagnosed participants. These results are summarised for both countries in Figure F-1.

During the three months of the study, some participants were permanently lost to follow-up, while others missed one or two appointments and later returned. The reasons for LTFU and the number of interviews completed at each time point are shown in Figure F-2 below. The majority of participants who were lost to follow-up completed only one interview. During the study eleven participants died and seven became unable to complete data collection. In most cases, the reason for non-completion was unknown.

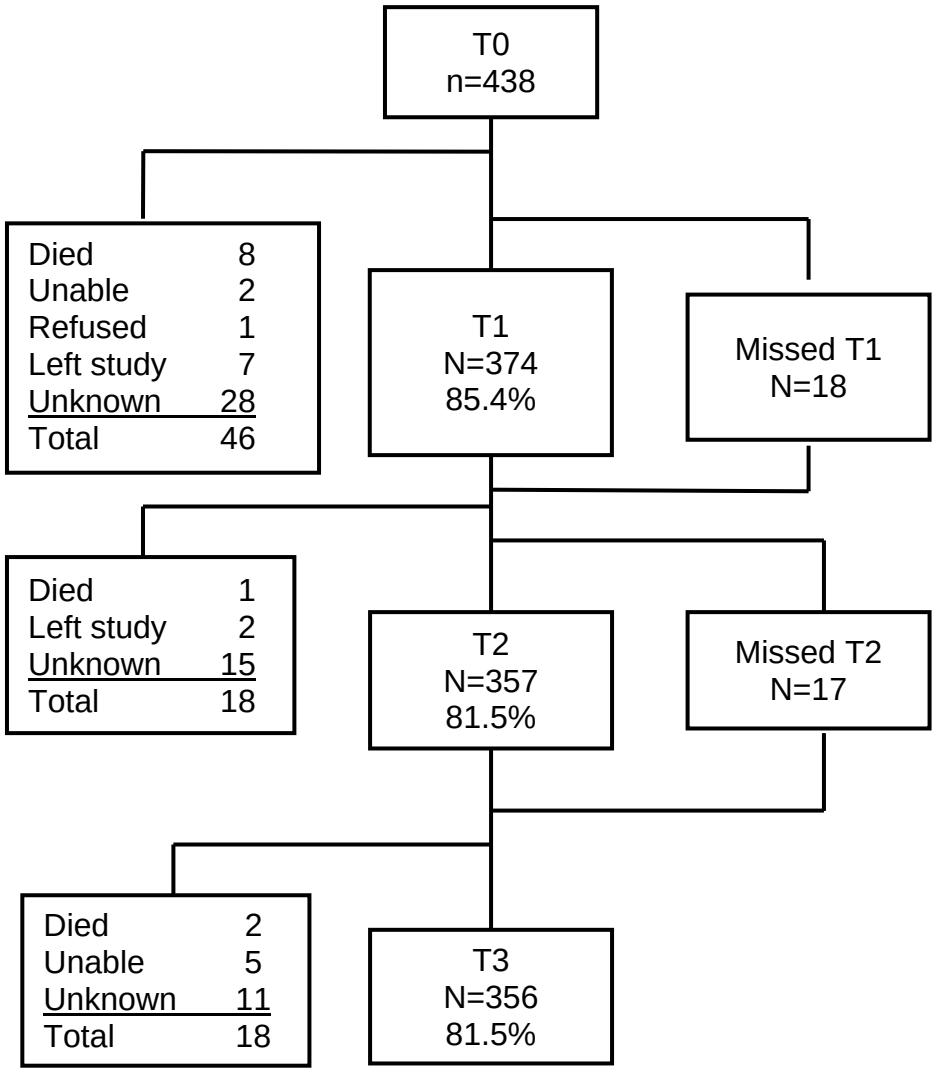
Of the 1593 data points collected, the patient was accompanied by a carer at 148 (9.3%). The proportion of patients with a carer present reduced over time, from 15.8% (n=72) at baseline to 9.0% (n=35) at T1, 6.2%(n=23) at T2 and 4.8% (n=18) at T3.

Figure F-1: results of 'newly diagnosed' decision tree



The twelve facilities selected for Phase 2 of the PEPFAR evaluation included one which did not recruit any new patients during the study period. This was site U6, in Uganda, which lacked funds to initiate any more patients onto ART in that year. The eleven facilities which contributed to the newly diagnosed group are listed in Table F-2 and named in Appendix C. K2 recruited only three newly diagnosed individuals during the study period. U2 recruited the most (80), due to its specialisation in voluntary counselling and testing. It also had a relatively high LTFU, which the staff explained was a consequence of its accessibility.

Figure F-2: flow diagram of interview completion



The study design indicated four equally spaced time points one month apart. The protocol specified that deviations of two weeks in either direction were acceptable. Some participants had longer periods of time between appointments. In Kenya, the civil unrest in January and February 2008 following a disputed presidential election caused widespread barriers to travel. Health facilities reportedly gave their patients two months' supplies of medication to enable them to stay at home.

Table F-2: interviews completed by facility

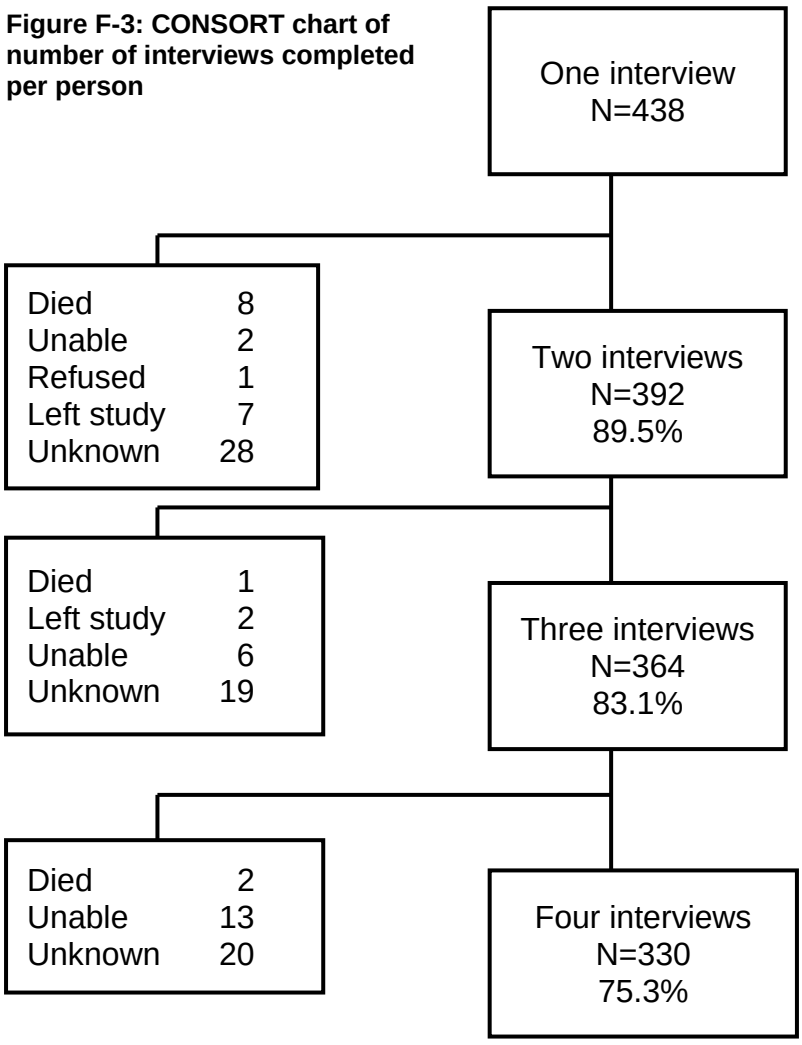
Facility	*Interviews completed at time point*			
	T0	**T1**	**T2**	**T3**
K1	40	40	39	37
K2	3	2	2	2
K3	76	65	61	61
K4	65	55	51	51
K5	24	18	16	16
K6	39	35	31	29
U1	18	17	17	17
U2	80	56	56	60
U3	27	26	24	22
U4	35	34	34	34
U5	31	26	26	27
Total	438	374	357	356

F.3 Preliminary recoding of the dataset

F.3.i Time interval recoding

In Figure F-3 below, the number of interviews completed by each person is represented, rather than the specific time points. While Figure F-2 showed that participants who had completed three interviews were very unlikely to fail to attend the fourth, Figure F-3 shows that 39 participants completed three interviews. This discrepancy is due to the number of participants who missed an interview and then returned.

Figure F-3: CONSORT chart of number of interviews completed per person



F.3.ii Other recoding

Participants occasionally reported that they did not known whether they had received a component of care for 13 of the 54 components, at seven of the facilities, as shown in Table F-3.

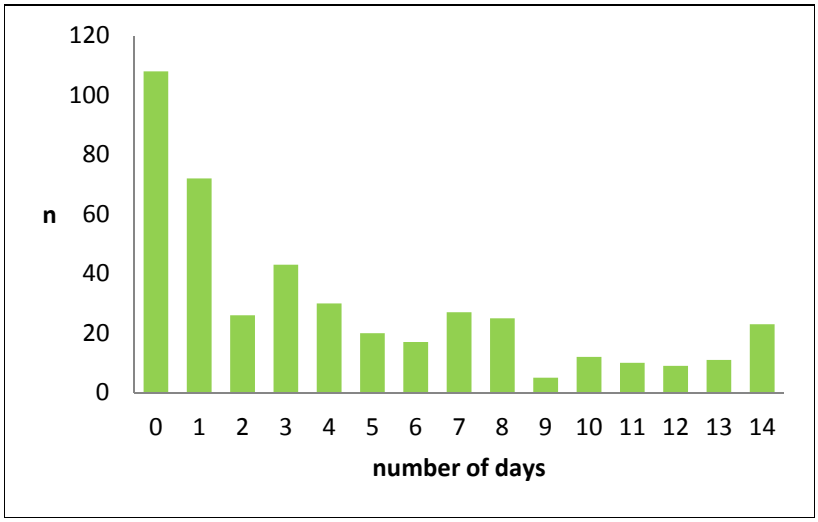
Table F-3: 'don't know' responses

Component	'Don't know' responses		Facility
	n	%	
Patient HIV support groups	5	0.3	U3
Prevention with positives	1	0.1	U2
ARVs	1	0.1	U3
Assessment of ARV treatment	1	0.1	U3
Assessment of pain	1	0.1	U2
Strong opioids	3	0.2	K5, U2, U3
Weak opioids	7	0.4	K5, U2, U3
Non-opioid analgesics	4	0.3	K1, U3
Treatment for oral candidiasis	1	0.1	K3
TB testing	1	0.1	K4
Treatment for other opportunistic infections	2	0.1	K1
Multivitamins	1	0.1	U3
Isoniazid	1	0.1	K3

F.4 Part A: Participant characteristics

In the 14 days before M0 438 participants were diagnosed, usually (78.3%) in the first week. The distribution of number of days from HIV diagnosis to recruitment was skewed to the left with the modal value being zero (Figure F-4). Participants consisted of 270 women (61.6%) and 168 men, aged 18 to 59 (mean 32.9).

Figure F-4: distribution of number of days from HIV diagnosis to M0



At recruitment, over two thirds of participants (69.9%) were fully active in terms of physical function using the ECOG scale(Table F-4). Most of the remainder were physically restricted but still able to carry out light work. More severe disability was rare (6.9% in total). It is unknown whether disability was caused by HIV or was incidental to it. No further details on its nature, cause or impact were collected.

Table F-4: physical function at T0

	n	%
Total	438	100.0
Fully active	306	69.9
Restricted in physically strenuous activity	102	23.3
Ambulatory but unable to work	23	5.3
Limited self-care	5	1.1
Completely disabled	2	0.5

Table F-5 shows the DHS Wealth index population characteristics. The average person lived in a home with a concrete floor, corrugated iron roof and walls made of

burnt brick or cement blocks, had some primary education, owned a radio and mobile phone, used a shared latrine, and cooked on charcoal or firewood. Time to travel from home to the health facility ranged from five minutes to six hours, with a third of respondents answering that it took one hour. Number of dependants ranged from none (for 11%) to 20, with a median of three.

Table F-5: demographic characteristics of newly diagnosed individuals

Population characteristic	N (%)
Highest level of schooling attended	
None	19 (4.3)
Began Primary	229 (52.3)
Began secondary	147 (33.6)
Diploma +	43 (9.8)
Wall material	
Thatch/mud and poles	115 (26.3)
Mud/unburnt bricks	27 (6.2)
Burnt bricks with mud	69 (15.8)
Metal sheet/cement block	101 (23.1)
Stone/wood/burnt bricks	126 (28.8)
Floor material	
Earth	138 (31.5)
Cement/concrete	281 (64.2)
Other finished	19 (4.3)
Roof material	
Natural	31 (7.1)
Corrugated iron	380 (86.8)
Finished	27 (6.2)
Type of toilet	
Private flush	44 (10.1)
Private VIP latrine	48 (11.0)
Traditional pit covered	98 (22.4)
Traditional pit uncovered	79 (18.0)
Public/shared	146 (33.3)
Bush/field/other	23 (5.3)
Source of drinking water	
Pipe-borne inside/bottle	74 (16.9)
Pipe-borne outside	174 (39.7)
Other safe	87 (19.9)
Other unsafe	103 (23.5)
Fuel Source	
Electricity/gas	21 (4.8)
Paraffin/coal	68 (15.5)
Charcoal	197 (45.0)
Firewood/straw/grass	148 (33.8)
Own car	51 (11.6)
Own bicycle	145 (33.1)
Own fridge	87 (19.9)
Own TV	189 (43.2)
Own mobile phone	322 (73.5)
Own radio	374 (85.4)

The information presented above on home construction, fuel, water and sanitation use, ownership of goods and education was used in a principal components analysis to generate a single factor which was then split into equal wealth quintiles. Details of how each component loaded onto the factor are presented in Appendix D. Table F-6 presents the percentage of participants reporting assets by quintile.

The lowest, poorest quintile was defined by having an earthen-floored home without a tiled roof, and by never possessing a car, refrigerator, flush toilet or indoor piped water. People who lived in a home built of poles and mud or thatch, cooked on firewood or drank unsafe water were normally in the lowest quintile. The second quintile was more likely to use bricks rather than poles and corrugated iron rather than thatch, and some of this group had outside piped water. The middle quintile was more likely than the second to have a cement or finished floor instead of earth. In the fourth quintile, some people had a finished (probably tiled) roof, the use of paraffin or coal became much more common, and ownership of televisions and refrigerators increased. This quintile also contained the most users of an outside or shared toilet. Two thirds of those who owned a car or refrigerator, three quarters of those who cooked on gas or electricity, almost everyone with a flush toilet and the majority of those with a tiled roof or finished floor were in the wealthiest quintile of the sample. Nobody in the wealthiest quintile used an unsafe water source or lived in a thatched home.

The variables with the greatest variation by quintile are those relating to home construction, a flush toilet, piped water, car ownership and use of electricity or gas. Bicycles and radios were similarly distributed across all five quintiles. A corrugated iron roof was also equally common regardless of quintile. Use of a public or shared latrine was about equally common in all groups except the highest quintile.

Table F-6: asset possession by socioeconomic quintile

	% respondents (n=438)				
	Wealth quintile				
Asset	*1 (lowest)*	*2 (second)*	*3 (middle)*	*4 (fourth)*	*5 (highest)*
Floor material					
Earth	63.8	32.6	2.9	0.7	0.0
Cement	0.0	15.3	28.5	30.3	26.0
Finished	0.0	0.0	15.8	15.8	68.4
Wall materials					
Thatch/mud & poles	63.5	29.6	3.5	3.5	0.0
Bricks – mud or unburnt	9.4	28.1	27.1	18.8	16.7
Metal sheet/cement block	1.0	12.9	18.8	26.7	40.6
Stone/wood/burnt bricks	4.0	11.1	30.2	31.8	23.0
Roof material					
Natural	83.9	6.5	3.2	6.5	0.0
Corrugated iron	16.1	22.6	22.6	22.1	16.6
Finished	0.0	0.0	0.0	11.5	88.5
Type of toilet					
Public/shared/outside	21.3	20.1	21.3	28.4	8.9
Latrine	23.1	23.6	22.7	17.3	13.3
Private flush	0.0	2.3	0.0	4.6	93.2
Source of drinking water					
Bottle/piped inside	0.0	9.5	14.9	5.4	70.3
Piped outside	0.6	16.7	26.4	38.5	17.8
Other, safe	25.3	35.6	20.7	14.9	3.5
Other, unsafe	63.1	20.4	11.7	4.9	0.0
Source of cooking fuel					
Electricity/gas	0.0	0.0	16.0	8.0	76.0
Paraffin/coal	1.5	7.4	16.2	39.7	35.3
Charcoal	1.5	19.3	28.4	29.4	21.3
Firewood/straw/grass	56.8	30.4	10.8	1.4	0.7
Household possessions					
Car	0.0	11.8	7.8	13.7	66.7
Bicycle	24.8	19.3	15.2	20.7	20.0
Refrigerator	0.0	2.3	5.8	25.3	66.7
Television	0.5	10.6	10.6	34.9	43.4
Mobile phone	11.8	14.9	21.1	25.8	26.4
Radio	19.5	19.0	18.2	21.4	21.9

F.4.i Kenya and Uganda compared

The populations from the two countries were compared in terms of demographic characteristics and measures of health at baseline in order to establish whether there were important differences or whether they could be treated as a single group (Table F-7).

Table F-7: comparison of Kenyan and Ugandan populations at baseline

		Kenya	Uganda
N		247	191
Gender (% female)		63.6	59.2
Age (mean, sd)		32.8 (8.7)	33.0 (8.3)
Education	-none	2.8	6.3
	-primary	57.1	46.4
	-secondary	31.6	35.5
	-diploma or higher	8.5	11.5
Days since diagnosis (median, IQR)		4 (1-8)	1 (0-5)
Has any recorded CD4 count (%)		92.3	51.3
Baseline CD4 count (median, IQR)		251 (100-407)	331 (188-488)
Wealth quintiles	-lowest	25.5	13.1
	-second	20.7	19.4
	-middle	16.2	24.6
	-fourth	17.4	24.1
	-highest	20.2	18.9

Median CD4 count was lower in Kenya than Uganda, but 92.3% of participants in Kenya had a baseline CD4 test result compared to only 51.3% in Uganda. At any time during the study, over 90% of people in Kenya had at least one CD4 test result, whereas almost half in Uganda never did. The two groups are therefore unlikely to be directly comparable, as the Kenya group includes the great majority of the study population, while the Uganda group comprises only half. The Kenya population were also significantly poorer, using the wealth quintiles described above, with an ANOVA test on a five per cent significance level ($F=4.89$, $p=0.028$). There was no significant association between country and educational attainment, gender or age.

F.5 Part A: Description of multidimensional problems at baseline

The results of the seven patient-completed items in the POS at study recruitment, up to 14 days after HIV diagnosis, are displayed in Table F-8.

Table F-8: POS scores at M0

POS item	% of individuals scoring (n=438)					
	0	*1*	*2*	*3*	*4*	*5*
Pain	33.1	22.6	24.9	13.2	5.3	0.9
Symptoms	34.3	28.5	22.8	11.2	2.1	1.1
Worry	31.5	22.4	26.0	9.4	5.7	5.0
Share feelings	11.6	7.1	12.8	15.5	21.0	32.0
Life worthwhile	42.7	21.2	14.8	11.2	5.0	5.0
Peace	24.4	21.7	23.1	11.6	8.0	11.2
Help and advice	8.7	6.9	7.8	12.1	17.4	47.3
Help and advice (if diagnosed >3 days before T0) *(n=189)*	11.6	7.4	9.0	12.2	15.3	44.4

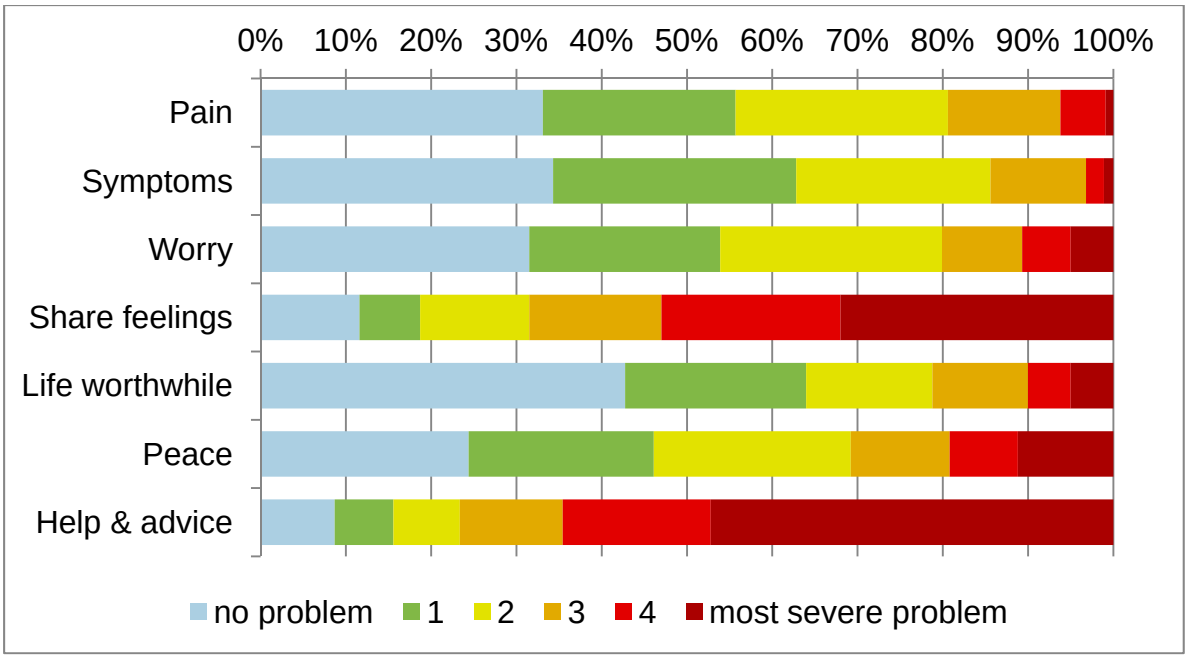
At recruitment, up to 14 days after HIV diagnosis, 19% of individuals experienced pain of 3, 4 or 5 in the previous three days. At the same time 14% reported scores of 3, 4 or 5 for symptoms; 20% for worry; 21% for difficulty finding life worthwhile; and 31% for peace. The highest burdens were found for problems sharing feelings, and need for help and advice. Over two thirds of participants (69%) reported this level of problems sharing their feelings, with almost a third (32%) not able to share their feelings at any time in the previous three days (score of 5). Almost half (47%) had received no help and advice (score of 5), and a further 29% scored 3 or 4.

The item regarding help and advice was analysed again for participants who had been diagnosed more than three days previously, on the grounds that the very recently diagnosed would not have been able to receive help before they knew their diagnosis. This restriction made a slight improvement to scores, but still left 44% who had received no help or advice in the previous three days.

The same information is presented graphically in Figure F-5. The figure shows that the distributions for the two items in the physical domain (pain and symptoms) were similar to each other, with around a third of participants reporting no problem and very few reporting the worst possible problem. Mild symptoms (the green and yellow

bars) were more common than mild pain. In the psychological domain, the distribution of worry scores was similar to that for pain, with the exception that very severe problems (red and dark red) were somewhat more common. Feeling life worthwhile was the area in which participants were most likely to record no problem at all, although more than half of responses did indicate a difficulty feeling worth in life. Severe and moderately severe problems occurred at the same frequency as for worry, but mild problems were less common. In the spiritual domain, over 10% of participants reported the worst possible score for difficulty feeling at peace. Peace scores were lower than scores for any of the psychological or physical items. However, the worst scores of all were for the two items in the social domain. Over 30% reported the worst possible score for difficulty sharing their feelings, and almost 50% for difficulty receiving help and advice for their family. The score distributions for these two items are clearly distinct from the pattern of the other five.

Figure F-5: POS scores at M0



The distribution of total POS scores at M0 is displayed in Figure F-6. The data appear to be Normally distributed with few data points in the very top end of the scale, which would signify the maximum possible level of problems. Of the 438 respondents 3.2% had a POS score below 5, 13.7% had a total POS score of 5 to 9,

36.2% scored 10 to 14, 31.8% scored 15 to 19, 13.3% scored 20 to 24 and 1.8% scored 25 to 35.

Figure F-6: distribution of total POS score at M0

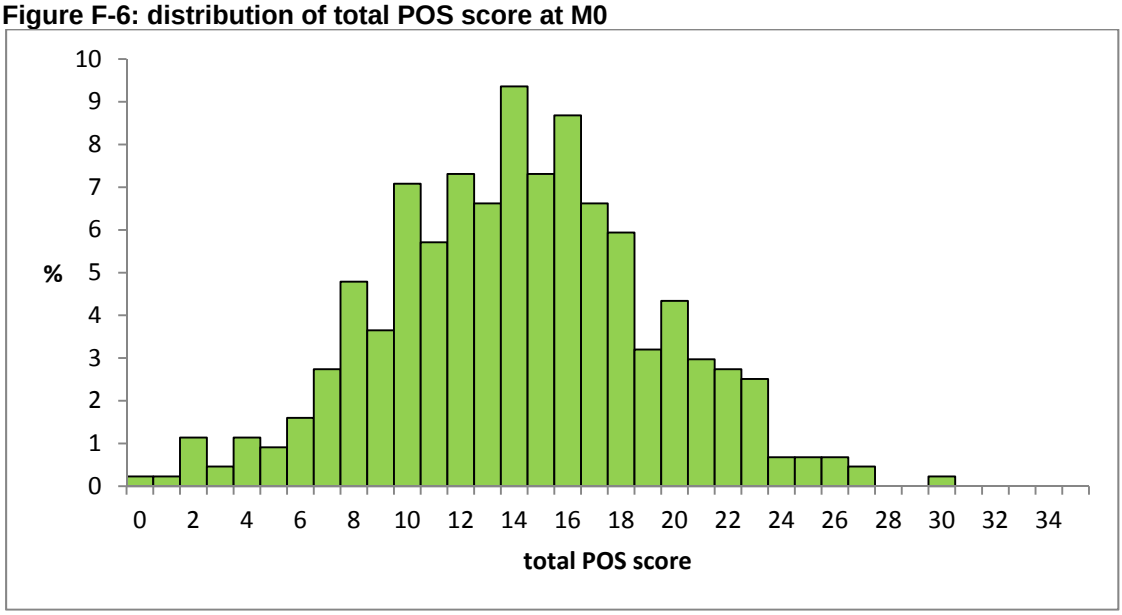


Figure F-6 illustrates that the proportion with no problems is very low. For example, although as shown in Figure F-5 approximately one third of participants have no pain, one third no symptoms, and one third no problems, only 7.1% (n=31) score 0 on all three of these items simultaneously.

F.6 Part B: Risk factors for multidimensional problems at baseline

Having established that multidimensional problems are highly prevalent in this recently diagnosed HIV-positive outpatient population, the second objective is to investigate whether demographic variables or CD4 count are associated with prevalence and severity of palliative care-related problems at diagnosis.

CD4 count was obtained for 297 participants (67.8%). Ternary POS item scores were tabulated against presence of a CD4 count at T0, to check for possible confounding, but association with presence of a CD4 count was not found for any outcome. Therefore CD4 count was included as a covariate for all seven outcomes.

F.6.i Pain

Table F-9 shows that pain is positively associated with limited physical function at the 10% level, and negatively associated with wealth. The data tabulations give more detailed information about these relationships. People with middle physical function are almost twice as likely to have severe pain, and half as likely to have no pain, as those with the best, while 30% of those with the worst physical function report severe pain. The association between wealth and pain is pronounced, but it is not perfectly linear. The fourth group actually has the highest prevalence of severe pain and does not fit the prevailing trend.

Table F-9: bivariate association of independent variables with pain severity

Variable	Value		Pain			Chi^2 test for association		NP test for trend	
			Low/ mild	Moderate	Severe	Chi^2	p	Z	p
		n	*244*	*167*	*27*				
Gender	Male	168	54.8	36.3	8.9	3.66	0.161		
	Female	270	56.3	39.3	4.4				
Age	18-25	89	62.9	29.2	7.9	4.81	0.308	1.47	0.140
	26-40	276	55.1	39.1	5.8				
	41-59	73	49.3	45.2	5.5				
Education	None	19	36.8	47.4	15.8	9.00	0.174	-2.03	0.042
	Primary	229	54.6	39.7	5.7				
	Secondary	147	55.8	38.8	5.4				
	Diploma+	43	69.8	23.3	7.0				
Wealth quintile	Lowest	88	45.5	47.7	6.8	26.24	0.001	-3.98	<0.001
	Second	88	40.9	53.4	5.7				
	Middle	87	60.9	34.5	4.6				
	Fourth	89	58.4	33.7	7.9				
	Highest	86	73.3	20.9	5.8				
Physical function	Best	306	66.0	30.4	3.6	67.98	<0.001	7.31	<0.001
	Middle	102	36.3	56.9	6.9				
	Worst	30	16.7	53.3	30.0				
Country	Kenya	247	58.3	35.2	6.5	2.03	0.363		
	Uganda	191	52.4	41.9	5.8				
		n	*171*	*109*	*17*				
CD4 count	0-100	70	18.7	29.4	35.3		0.077*	-1.85	0.064
	101-200	47	18.1	14.7	0				
	201-350	71	22.2	26.6	23.5				
	350+	109	40.9	29.4	41.2				

*Fisher's exact test

The non-parametric test for trend shows a significant association with education, suggesting that those with less education are more likely to have pain, but this finding is not significant using a chi^2 test. Observation of the data suggests it may be driven by the unusually high proportion reporting severe pain in the lowest education level (15.8%, compared to a range of 5.4-7% in the other education levels).

It is a general rule that greater wealth is associated with better education. To test the hypothesis that the observed association with education was confounded by wealth, the two variables were tabulated.

Table F-10: distribution of education over wealth quintile (%)

Wealth quintile		Education level				
		None	Primary	Secondary	Diploma+	Total
	n	19	229	147	43	438
Lowest	88	7.8	68.2	19.3	4.6	100.0
Second	88	5.7	70.5	20.5	3.4	100.0
Middle	87	3.5	42.5	47.1	6.9	100.0
Fourth	89	4.5	49.4	38.2	7.9	100.0
Highest	86	0	30.2	43.0	26.7	100.0

Table F-10 shows a clear linear trend, with wealthier people more likely to have more formal education. A chi squared test found very strong evidence for an association between the two variables (chi^2=76.28, p<0.001).

Next, stratum-specific estimates for the odds ratio (OR) for the effect of education on pain prevalence by wealth quintile were calculated. The summary adjusted OR was compared with the unadjusted OR of the effect of education on pain prevalence, in order to determine whether wealth confounded the relationship between education and pain.

Table F-11: the association of pain prevalence with education, by wealth quintile

Wealth quintile	n	Log OR	OR for effect of education on pain	Z	p	95% CI of OR
All (unadjusted)	438	-0.273	0.76	-2.05	0.040	0.59-0.99
Lowest	88	-0.163	0.85	-0.48	0.630	0.44-1.65
Second	88	0.039	1.04	0.11	0.909	0.53-2.05
Middle	87	0.219	1.25	0.67	0.503	0.66-2.37
Fourth	89	-0.204	0.82	-0.67	0.504	0.45-1.48
Highest	86	-0.142	0.87	-0.44	0.663	0.46-1.64

In Table F-11, the unadjusted OR for the effect of education on pain is 0.76, with a p-value of 0.040. The stratum-specific ORs are all closer to zero than the unadjusted value, some higher and some lower, with no discernible trend. Wealth quintile appears to completely confound the apparent relationship between education and pain. Education was therefore dropped from the analysis.

To test whether wealth and physical function were associated with each other, the two were tabulated (Table F-12), showing that poorer people were more likely to have limited physical function (ch^{i2}=17.65, p=0.024). These results were even more apparent using a non-parametric test for trend (z=-2.37, p=0.018).

Table F-12: distribution of wealth quintiles over physical function (%)

Wealth quintile		Physical function			
		Best	**Middle**	**Worst**	**total**
	n	306	102	30	438
Lowest	88	69.3	25.0	5.7	100.0
Second	88	53.4	34.1	12.5	100.0
Middle	87	72.4	23.0	4.6	100.0
Fourth	89	78.7	15.7	5.6	100.0
Highest	86	75.6	18.6	5.8	100.0

To test both for trend and for interaction, stratum-specific ORs were calculated for the effect of physical function on pain, within each wealth quintile.

Table F-13: the association of pain prevalence with physical function, by wealth quintile

Wealth quintile	Log OR	ORs for effect of physical function on pain severity	Z	p	95% CI of ORs
All (unadjusted)	1.203	3.33	7.24	<0.001	2.40-4.61
Lowest		2.05	1.97	0.049	1.00-4.19
Second		2.30	2.52	0.012	1.20-4.40
Middle		4.92	2.07	<0.001	2.16-11.24
Fourth		3.94	3.41	0.001	1.79-8.66
Highest		5.01	3.93	<0.001	2.24-11.20

Table F-13 shows that the unadjusted OR for the effect of physical function on pain was 3.33 ($p<0.001$); an increase of 1 in physical impairment score more than tripled the odds of pain. Stratum-specific ORs for the effect of physical function on pain ranged from 2.05 to 5.01, with wide confidence intervals (Table F-13). There was no evidence for a confounding effect of wealth on the relationship between physical function and odds of pain.

A ordinal logistic regression (OLR) model was fitted, first using indicator variables to model the independent variables as categorical, and then treating them as ordinal. The covariates were physical function, wealth quintile, and Cd4 count, but CD4 count was found to be no longer associated with pain so it was dropped. The categorical model showed clear trends which were supported in the ordinal model, and the log likelihoods were not significantly different ($chi2=3.61$, $p=0.307$). The simpler ordinal model was therefore accepted and is reproduced below (Table F-14).

Table F-14: association of physical function and wealth quintile with pain severity using OLR

	Log OR	SE	Z	p	OR	95% CI of OR
Physical function	1.160	0.167	6.93	<0.001	3.19	2.30-4.43
Wealth quintile	-0.235	0.071	-3.29	0.001	0.79	0.69-0.91

The results in Table F-14 show that one point on the ECOG scale was associated with a threefold increase in the odds of moderate pain compared to mild or severe pain compared to moderate. An increase in wealth quintile was associated with reduced odds of pain. The effect of wealth was much weaker than the effect of physical function but still highly significant.

F.6.ii Symptoms

Only 14 people report severe symptoms, which is the lowest prevalence of severe problems of any outcome. As a result, all four of the non-binary independent variables fail to meet the validity requirements of a chi-square test here, either because more than a fifth of the table cells have an expected value below five (age and wealth quintile) or because a cell has an expected value below one (education and physical function). Fisher's exact test was used instead. The 5x3 table of wealth quintile against symptom score was too large to calculate Fisher's exact test, using the maximum memory which my PC's operating system would allocate to Stata (512Mb). The non-parametric test for trend indicates a probable association with symptom prevalence.

Prevalence and severity of symptoms are associated with wealth quintile, education and physical function. Poorer people and those with less education are more likely to report symptoms. Symptoms are also more common among people with limited physical function, especially those in the worst group.

Table F-15:bivariate association of independent variables with symptom severity

Variable	Value		Symptoms			Chi^2 test for association		NP test for trend	
			Mild/ none	Moderate	Severe	Chi^2	p	Z	p
		n	*275*	*149*	*14*				
Gender	Male	168	59.5	38.1	2.4	2.36	0.307		
	Female	270	64.8	31.5	3.7				
Age	18-25	89	64.0	31.5	4.5		0.608*	0.84	0.401
	26-40	276	64.1	33.0	2.9				
	41-59	73	56.2	41.1	2.7				
Education	None	19	47.4	36.8	15.8		0.028*	-1.88	0.060
	Primary	229	62.9	34.1	3.1				
	Secondary	147	59.9	38.1	2.9				
	Diploma+	43	79.1	18.6	2.3				
Wealth quintile	Lowest	88	59.1	37.5	3.4		-	-2.60	0.009
	Second	88	51.1	44.3	4.6				
	Middle	87	65.5	29.9	4.6				
	Fourth	89	65.2	33.7	1.1				
	Highest	86	73.3	24.4	2.3				
Physical function	Best	306	73.5	24.5	2.0		<0.001*	7.12	<0.001
	Middle	102	40.2	56.9	2.9				
	Worst	30	30.0	53.3	16.7				
Country	Kenya	247	65.2	31.6	3.2	1.51	0.469		
	Uganda	191	59.7	37.2	3.1				
		N	*188*	*98*	*11*				
CD4 count	0-100	70	16.5	33.7	54.6		0.009*	-3.15	0.002
	101-200	47	17.0	14.3	9.1				
	201-350	71	27.1	18.4	18.2				
	350+	109	39.4	33.7	18.2				

*Fisher's exact test

Wealth and physical function are both associated with pain as well as symptoms. In Section 0 above, they were tabulated (Table F-12), showing a statistically significant association between them (chi^2=17.65, p=0.024). Education is also associated with wealth quintile, as seen in Table F-10 (chi^2=76.28, p<0.001).

The association of physical function and wealth quintile with symptom prevalence was analysed using stratum-specific ORs. The results (Table F-16) show that the OR for the effect of physical function on symptom prevalence increases with wealth from 1.35 to 5.47, suggesting an interaction relationship. This is the same tendency that

was observed in the stratum-specific ORs for pain prevalence in Table F-13, but it is more pronounced.

Table F-16: Association of symptom prevalence with physical function, by wealth quintile

Wealth quintile	Log OR	ORs for the effect of physical function on symptom prevalence	z	p	95% CI of ORs
All (unadjusted)	1.172	3.23	6.89	<0.001	2.32-4.51
Lowest	0.300	1.35	0.85	0.397	0.67-2.70
Second	0.884	2.42	2.70	0.007	1.27-4.60
Middle	1.709	5.23	3.93	<0.001	2.36-12.95
Fourth	1.619	5.05	3.40	0.001	1.99-12.83
Highest	1.699	5.47	3.95	<0.001	2.35-12.70

Next, the effect of education on the odds of symptoms was examined by wealth quintile, showing that after adjusting for wealth, the association between education and symptoms was weak and non-significant (Table F-17). This was the same result as had been found in the pain analysis. Accordingly, education was dropped from the model.

Table F-17: the association of symptom prevalence with education, by wealth quintile

Wealth quintile	Log OR	OR for the effect of education on symptoms	z	p	95% CI of ORs
All (unadjusted)	-0.264	0.77	-1.90	0.058	0.58-1.01
Lowest	-0.022	0.98	-0.07	0.948	0.50-1.90
Second	-0.149	0.86	-0.42	0.676	0.43-1.73
Middle	-0.197	0.82	-0.57	0.571	0.41-1.63
Fourth	-0.148	0.86	-0.47	0.641	0.46-1.61
Highest	-0.149	0.86	-0.46	0.647	0.46-1.63

An OLR model was fitted with physical function, wealth quintile and CD4 count as covariates, using indicator variables and an interaction term, Both the interaction and CD4 count proved non-significant so they was removed. Then the model was compared with one fitting the independent variables as ordinal. The second model was as representative as the first, and simpler, so it was accepted.

Table F-18: association of physical function and wealth quintile with symptom severity using OLR

	Log OR	SE	Z	p	OR	95% CI of ORs
Physical function	1.148	0.171	6.72	<0.001	3.15	2.26-4.41
Wealth quintile	-0.147	0.074	-2.00	0.046	0.86	0.75-1.00

Table F-18 shows that the results for symptoms were similar to the results for pain; a strong association with physical function (limited function increasing the odds of symptoms) and a weak association with wealth quintile, in the opposite direction (wealth decreasing odds of symptoms).

F.6.iii Worry

Table F-19: bivariate association of independent variables with worry severity

Variable	Value		Worry			Chi^2 test for association		NP test for trend	
			Mild/ none	Moderate	Severe	Chi^2	p	Z	p
		n	*236*	*155*	*47*				
Gender	Male	168	61.9	28.0	10.1	7.58	0.023		
	Female	270	48.9	40.0	11.1				
Age	18-25	89	55.1	33.7	11.2	0.27	0.992	0.10	0.922
	26-40	276	53.6	35.5	10.9				
	41-59	73	53.4	37.0	9.6				
Education	None	19	57.9	26.3	15.8	5.90	0.435	1.62	0.105
	Primary	229	57.2	33.2	9.6				
	Secondary	147	51.7	36.1	12.2				
	Diploma+	43	41.9	48.8	9.3				
Wealth quintile	Lowest	88	56.8	33.0	10.2	9.52	0.300	0.70	0.481
	Second	88	50.0	37.5	12.5				
	Middle	87	57.5	29.9	12.6				
	Fourth	89	60.7	34.8	4.5				
	Highest	86	44.2	41.9	14.0				
Physical function	Best	306	57.2	35.0	7.8	11.54	0.021	2.83	0.005
	Middle	102	48.0	36.3	15.7				
	Worst	30	40.0	36.7	23.3				
Country	Kenya	247	57.1	32.4	10.5	2.54	0.281		
	Uganda	191	49.7	39.3	11.0				
	n	*168*	*102*	*27*					
CD4 count	0-100	70	24.4	22.6	3.14	0.791	1.04	0.297	
	101-200	47	17.9	11.8					
	201-350	71	24.4	23.5					
	350+	109	33.3	42.2					

Table F-19 above shows that two independent variables are associated with worry at the 10% level. Women have a higher probability than men of experiencing moderate worry, but not severe worry, where the proportions are very similar. Also there is a clear trend for poor physical function to be associated with greater prevalence of worry and with more severe worry. There is no discernible relationship between worry and wealth quintile, although a bivariate trend was seen previously for both pain and symptoms.

The two variables gender and physical function were tabulated in order to detect any association between them (Table F-20). Using two degrees of freedom, a chi^2 test found no association between the variables (chi^2=1.29, p=0.526). Therefore it would not be possible for either of them to confound the association between the other and worry.

Table F-20: distribution of gender over physical function (%)

Gender		Physical function			
		Best	**Middle**	**Worst**	**Total**
	n	306	102	30	438
Male	168	67.3	24.4	8.3	100.0
Female	270	71.5	22.6	5.9	100.0

To test for interaction, the stratum-specific ORs of worry for women compared to men were calculated for each level of physical function (Table F-21). The results show that the association between gender and worry is only significant for participants with the best physical health and disappears entirely for those with the worst. The possibility of interaction was investigated further.

Table F-21: association of prevalence of worry with gender, by physical function

Physical function	Log OR	OR for the effect of gender on worry	z	p	95% CI of ORs
All (unadjusted)	0.466	1.59	2.39	0.017	1.09-2.34
Best	0.575	1.78	2.39	0.017	1.11-2.84
Middle	0.374	1.45	0.96	0.337	0.68-3.12
Worst	0.016	1.02	0.02	0.982	0.26-3.96

The first OLR model included an interaction term between physical function and gender. The interaction term ORs were small and non-significant, and the likelihood

ratio test showed they were not beneficial. A further model showed that physical function could be modelled as linear, rather than categorical (while gender was coded 0/1 and so using indicator variables made no difference to it). This simplest, most efficient model was retained to represent the data and is shown below(Table F-22). Each level of limitation in physical function (from best to middle, or from middle to worst) increases the odds of worry by 1.56. Women have significantly higher odds of worry than men.

Table F-22: association of physical function and gender with worry severity using OLR

	Log OR	SE	Z	p	OR	95% CI of OR
Physical function	0.446	0.153	2.91	0.004	1.56	1.16-2.11
Gender	0.489	0.196	2.45	0.014	1.62	1.10-2.37

These results should be compared with the prevalence figures in Table F-19 above. People with severe worry constitute 6% of the total sample but 30% of those with the worst physical function, making impaired physical function strongly predictive of severe worry in this small group. Men and women have a similar prevalence of severe worry, but 40% of women, compared to 28% of men, report moderate worry. The interpretation of these findings is that at HIV diagnosis women are more likely to be worried than men, but the people at greatest risk of severe, complex worry, regardless of gender, are those with the most limited physical function.

F.6.iv Difficulty sharing feelings

Table F-23: bivariate association of independent variables with severity of problems sharing feelings

Variable	Value		Problems sharing feelings			Chi^2 test for homogeneity		NP test for trend	
			Mild/ none	Moderate	Severe	Chi^2	p	Z	p
		n	*82*	*124*	*232*				
Gender	Male	168	23.2	33.3	43.5	10.03	0.007		
	Female	270	15.9	25.2	58.9				
Age	18-25	89	11.2	24.7	64.0	6.69	0.153	2.22	0.027
	26-40	276	20.7	28.6	50.7				
	41-59	73	20.6	31.5	48.0				
Education	None	19	15.8	26.3	57.9	5.86	0.439	-1.09	0.274
	Primary	229	18.8	28.4	52.8				
	Secondary	147	15.7	27.9	56.5				
	Diploma+	43	30.2	30.2	39.5				
Wealth quintile	Lowest	88	22.7	34.1	43.2	16.12	0.041	0.54	0.588
	Second	88	22.7	23.9	53.4				
	Middle	87	11.5	23.0	65.5				
	Fourth	89	12.4	29.2	58.4				
	Highest	86	24.4	31.4	44.2				
Physical function	Best	306	15.4	25.8	58.8	23.65	<0.001	-4.63	<0.001
	Middle	102	21.6	33.3	45.1				
	Worst	30	43.3	36.7	20.0				
Country	Kenya	247	19.0	21.9	59.1	12.38	0.002		
	Uganda	191	18.3	36.7	45.0				
		N	*168*	*82*	*47*				
CD4 count	0-100	70	20.8	24.4	31.9	11.32	0.079	-1.70	0.089
	101-200	47	15.5	17.1	14.9				
	201-350	71	25.0	15.9	34.0				
	350+	109	38.7	42.7	19.2				

Four independent variables are associated with this outcome in bivariate analysis (Table F-23). Women report more difficulty sharing their feelings than men, there is a trend for younger people to have more problems than older people, and Kenyans have more problems than Ugandans. Finally, people with impaired physical function have fewer problems sharing their feelings than people with the best. This is surprising, as all other dependent variables examined so far (pain, symptoms, and worry) are negatively associated with physical function. Wealth is significantly different from the expected distribution on a chi squared test but there is no directional trend, so the association is thought to be coincidental.

The 41-59 age group is mostly male (64%) while 81% of the 18-25 group is female. There is a clear trend for men to be older than women (chi^2=34.92, p<0.001), as is usual for an HIV-positive population in Africa. Since age is associated with gender, confounding is a possibility. Stratum-specific ORs for the association of gender with difficulty sharing feelings were calculated and compared with the unadjusted OR(Table F-24). A significant association was only observed in the 26-40 age group. This is the largest group, which makes statistical significance more likely, but the associations in the other age groups were also weaker (ORs closer to 1).

Table F-24: association of difficulty sharing feelings with gender, by age category

Age category	Log OR	OR for the effect of gender on difficulty sharing feelings	z	p	95% CI of OR
All (unadjusted)	0.577	1.78	3.09	0.002	1.24-2.57
18-25	0.131	1.14	0.25	0.805	0.40-3.21
26-40	0.615	1.85	2.63	0.009	1.17-2.94
41+	0.405	1.50	0.88	0.380	0.60-3.74

Gender, age, physical function, CD4 count and country were taken forward into OLR to determine whether they were associated with the severity of problems. At first, an interaction term between gender and age was included, but it was found not to be significant. Country, age and CD4 count were also dropped from the model, and physical function was more efficiently modelled as linear. The final model is shown in Table F-25.

Table F-25: association of physical function and gender with difficulty sharing feelings using OLR

	Log OR	SE	Z	p	OR	95% CIs of OR
Gender	0.558	0.189	2.95	0.003	1.75	1.21-2.53
Physical function	-0.670	0.149	-4.50	<0.001	0.51	0.38-0.69

As shown in Table F-23, 59% of people with the best physical function have great difficulty sharing feelings, compared to 45% of the middle group and only 20% of the worst. It is not clear why limitation to physical function should improve the ability to share feelings, or whether the result is driven by a confounding variable. The ‘worst function’ group is very small (30 people) and so the possibility of spurious results is increased. However, the trend continues in the larger ‘middle function’ group, which adds credibility to the finding.

F.6.v Difficulty finding life worthwhile

Table F-26: bivariate association of independent variable with severity of difficulty feeling life worthwhile

Variable	Value		Problems feeling life worthwhile			Chi^2 test for association		NP test for trend	
			None/ mild	Moderate	Severe	Chi^2	p	Z	p
		n	*280*	*114*	*44*				
Gender	Male	168	68.5	22.6	8.9	2.43	0.297		
	Female	270	61.1	28.2	10.7				
Age	18-25	89	52.8	32.6	14.6	16.95	0.002	-2.51	0.012
	26-40	276	64.9	27.9	7.3				
	41-59	73	74.0	11.0	15.1				
Education	None	19	52.6	31.6	15.8		0.658*	-1.58	0.113
	Primary	229	62.5	28.0	9.6				
	Secondary	147	64.6	24.5	10.9				
	Diploma+	43	74.4	18.6	7.0				
Wealth quintile	Lowest	88	51.1	37.5	11.4	14.22	0.076	-3.08	0.002
	Second	88	60.2	27.3	12.5				
	Middle	87	67.8	24.1	8.1				
	Fourth	89	65.2	25.8	9.0				
	Highest	86	75.6	15.1	9.3				
Physical function	Best	306	67.3	21.9	10.8	13.81	0.008	2.40	0.016
	Middle	102	60.8	31.4	7.8				
	Worst	30	40.0	50.0	10.0				
Country	Kenya	247	71.3	19.0	9.7	15.48	<0.001		
	Uganda	191	54.5	35.1	10.5				
		n	*205*	*62*	*30*	3.70	0.717	-0.30	0.762
CD4 count	0-100	70	23.9	22.6	23.3				
	101-200	47	16.1	16.1	13.3				
	201-350	71	21.0	29.0	33.3				
	350+	109	39.0	32.3	30.0				

* Fisher's exact test

Table F-26 shows that younger people, poorer people, people with limited physical function and Ugandans are less likely to feel life worthwhile. The trends are much more evident for the none/mild and moderate categories than for the severe category. For example, there is a consistent pattern that with every increase in age group, the proportion of people reporting no or mild problem feeling life worthwhile decreases and the proportion reporting a moderate problem increases. However, the proportion reporting a severe problem does not fit this relationship. The same is true for the association between physical function and outcome.

Table F-12 above showed that wealth quintile and physical function are associated with each other in a negative trend (z=-2.37, p=0.018). It seems likely that confounding might exist. Since wealth quintile is the variable more strongly associated with this outcome, it is more likely to be a confounder. Stratum-specific ORs for the effect of physical function on feeling life worthwhile were calculated by wealth quintile. The results are shown in Table F-27. There is an approximate trend for physical function to have more effect on outcome with higher wealth, but the 95% confidence intervals of the odds ratios overlap. One stratum (the fourth) has a much higher OR than average and is the only one to show a statistically significant association with physical function. This could be a chance event. There is not enough evidence for effect modification to justify adding in the complexity of an interaction term, therefore wealth quintile and physical function continue to be treated as separate independent variables.

Table F-27: association of prevalence of problems feeling life worthwhile with physical function, by wealth quintile

Wealth quintile	Log OR	OR for effect of physical function on difficulty finding life worthwhile	z	p	95% CI of OR
All (unadjusted)	0.352	1.42	2.33	0.020	1.06-1.91
Lowest	-0.215	0.81	-0.62	0.532	0.41-1.58
Second	0.090	1.09	0.29	0.769	0.60-2.00
Middle	0.209	1.23	0.55	0.580	0.59-2.58
Fourth	1.278	3.59	3.47	0.001	1.74-7.38
Highest	0.448	1.57	1.20	0.231	0.75-3.26

The four independent variables age, physical function, wealth quintile and country were used in ordinal logistic regression. Indicator variables were used first but a linear model proved equally effective (chi^2=2.67, p=0.751). Physical function was no longer significantly associated with the outcome after adjusting for country, relative wealth and age.

Table F-28: association of country, wealth quintile, physical function and age with severity of problems feeling life worthwhile using OLR

	Log OR	SE	Z	p	OR	95% CI of OR
Country	0.705	0.205	3.45	<0.001	2.10	1.41-3.12
Wealth quintile	-0.245	0.073	-3.36	0.001	0.78	0.68-0.90
Age	-0.417	0.169	-2.46	0.014	0.66	0.47-0.92

Table F-28 shows that finding life worthwhile is most closely associated with country (OR=2.10), with problems more common in Uganda than Kenya. Increasing wealth and age reduce the odds of problems.

F.6.vi Difficulty finding peace

Table F-29: bivariate association of independent variables with severity of problems feeling at peace

Variable	Value		Problems feeling at peace			Chi^2 test for association		NP test for trend	
			Mild/ none	Moderate	Severe	Chi^2	p	Z	p
		n	*202*	*152*	*84*				
Gender	Male	168	46.4	35.7	17.9	0.33	0.846		
	Female	270	45.9	34.1	20.0				
Age	18-25	89	42.7	36.0	21.4	20.42	<0.001	-3.22	0.001
	26-40	276	40.9	37.7	21.4				
	41-59	73	69.9	21.9	8.2				
Education	None	19	63.2	21.1	15.8	5.10	0.531	1.82	0.069
	Primary	229	48.9	32.8	18.3				
	Secondary	147	41.5	38.1	20.4				
	Diploma+	43	39.5	39.5	20.9				
Wealth quintile	Lowest	88	48.9	30.7	20.5	1.33	0.995	0.29	0.772
	Second	88	45.5	35.2	19.3				
	Middle	87	44.8	36.8	18.4				
	Fourth	89	47.2	36.0	16.9				
	Highest	86	44.2	34.9	20.9				
Physical function	Best	306	51.0	33.0	16.0	16.94	0.002	4.00	<0.001
	Middle	102	40.2	36.3	23.5				
	Worst	30	16.7	46.7	36.7				
Country	Kenya	247	56.7	27.5	15.8	25.49	<0.001		
	Uganda	191	32.5	44.0	23.6				
		n	*151*	*101*	*45*	4.91	0.555	0.17	0.863
CD4 count	0-100	70	23.8	21.8	26.7				
	101-200	47	16.6	11.9	22.2				
	201-350	71	25.8	23.8	17.8				
	350+	109	33.8	42.6	33.3				

Table F-29 shows that older people are more likely to feel at peace. Specifically, those aged over 40 are more likely to feel at peace. The percentage figures show that the two younger groups are similar to each other in score distribution, with 21% having severe problems and 41-43% mild problems, but the over-40 group has only an 8% prevalence of severe problems. Better physical function is also associated

with fewer problems finding peace, and Ugandans are significantly more likely than Kenyans to say they did not feel at peace. It is interesting to note that there is no evidence associating wealth quintile with peace, although Table F-26 shows that wealthier people are more likely to say they find life worthwhile.

Any association between physical function and age is likely to be negative rather than positive, both because of increased probability of disability with age, and the probability of more advanced HIV progression. However, the two variables affect peace in opposite directions; age positively, and physical function negatively. Therefore it is unlikely they confound each other. The age of the populations in the two countries is known to be similar (Table F-7) and so they also cannot be confounders.

All three variables were included in OLR. Initially physical function and age were modelled as categorical variables, but physical function proved to show a consistent trend which was modelled equally well as an ordinal variable. Age remained a categorical variable because the results for the strata were very different and the ordinal model had a significantly lower log likelihood (chi^2=11.81, p=0.003).

Table F-30: association of physical function, age and country with severity of problems finding peace, using OLR

	Log OR	SE	Z	p	OR	95% CI of OR
Physical function	0.531	0.149	3.56	<0.001	1.70	1.27-2.28
Age:						
26-40	0.078	0.232	0.34	0.736	1.08	0.69-1.70
41-59	-1.195	0.329	-3.63	<0.001	0.30	0.16-0.58
Country	0.838	0.188	4.46	<0.001	2.31	1.60-3.34

The results show that limited physical function and being in Uganda are associated with increased odds of problems feeling at peace (Table F-30). Those aged over 40 have fewer problems, but the other two age groups are no different from each other. Being aged over 40 has the strongest association with the outcome (OR=0.30), followed by country (OR=2.31, or 0.43 when reversed).

F.6.vii Difficulty obtaining help and advice

Table F-31: bivariate association of independent variables with need for help and advice

Variable	value	Need for help and advice				Chi^2 test for association		NP test for trend	
			None/ mild	Moderate	Severe	Chi^2	p	Z	p
		n	*68*	*87*	*283*				
Gender	Male	168	16.1	22.0	61.9	1.00	0.606		
	Female	270	15.2	18.5	66.3				
Age	18-25	89	14.6	25.8	59.6	3.50	0.478	0.12	0.905
	26-40	276	14.9	18.1	67.0				
	41-59	73	19.2	19.2	61.6				
Education	None	19	0	26.3	73.7	37.28	<0.001	-4.32	<0.001
	Primary	229	11.4	17.5	71.2				
	Secondary	147	23.1	15.0	61.9				
	Diploma+	43	18.6	46.5	34.9				
Wealth quintile	Lowest	88	14.8	18.2	67.1	17.22	0.028	-2.49	0.013
	Second	88	12.5	19.3	68.2				
	Middle	87	11.5	17.2	71.3				
	Fourth	89	12.4	18.0	69.7				
	Highest	86	26.7	26.7	46.5				
Physical function	Best	306	14.4	17.3	68.3	10.66	0.031	-2.57	0.010
	Middle	102	14.7	27.5	57.8				
	Worst	30	30.0	20.0	50.0				
Country	Kenya	247	22.7	19.4	57.9	22.64	<0.001		
	Uganda	191	6.3	20.4	73.3				
		n	*52*	*66*	*179*				
CD4 count	0-100	70	30.8	22.7	21.8	2.00	0.920	0.17	0.863
	101-200	47	13.5	16.7	16.2				
	201-350	71	23.1	22.7	24.6				
	350+	109	32.7	37.9	37.4				

Table F-31 shows that problems getting enough help and advice are more likely for people with less education, less wealth and better physical function, and for people in Uganda.

The percentage figures in Table F-31 show that the prevalence of severe problems by wealth quintile is fairly uniform, apart from the highest quintile, where the distribution is very different. In the other four quintiles the prevalence of severe problems ranges in a tight band from 67% to 71%, while the highest quintile has a prevalence of 47%. To test this, the non-parametric test for trend was repeated using wealth quintile without the highest quintile, and the trend disappeared (p=0.59),

showing that it had been driven only by that difference. Only the wealthiest fifth of the population benefit in terms of having fewer problems receiving help and advice.

Kenya is a more affluent country than Uganda, and more of the Kenya facilities are in urban areas. To test whether country confounds the unexpected relationship between wealth and the outcome, wealth quintile was tabulated against country (Table F-32). Ugandans are more likely to appear in the middle and fourth quintiles than Kenyans, and there is a positive overall trend, with Ugandans more likely to be wealthy. When analysed using both a chi squared test and a test for trend, the probability of obtaining these findings by chance is lower in the chi^2 test, which does not detect direction, than in the trend test (chi^2=14.66, p=0.005; z=2.20, p=0.028). This suggests that the distribution is different from what would be expected by chance, but the difference is without clear direction. The unusual findings in the lowest quintile, with only 13% of Uganda respondents grouped with 26% of Kenyans, probably contribute substantially to the trend result. As shown by this example and the previous one, tests for trend are vulnerable to reporting overall trends when the first or last stratum is very different from the average.

Table F-32: distribution of country of data collection over wealth quintile

Country		Wealth quintile					
		Lowest	**Second**	**Middle**	**Fourth**	**Highest**	**Total**
	n	88	88	87	89	86	438
Kenya	247	25.5	20.7	16.2	17.4	20.2	100.0
Uganda	191	13.1	19.4	24.6	24.1	18.9	100.0

Table F-10 in Section F.6.i shows the association between education and wealth quintile. In particular, the highest quintile has an unusual education distribution. While there is a clear trend throughout the table, the richest quintile displays much more extreme values than a linear trend would predict. Everyone in the highest quintile has some education and 27% have a diploma or degree, while the next highest proportion is 9%.

Earlier, in the analysis of pain, the apparent relationship between education and pain proved to be totally confounded by wealth (Table F-11). Here, it seemed possible

that the apparent relationship between wealth and problems receiving help is confounded by education. To test this, stratum-specific ORs were calculated to show the effect of wealth quintile on the outcome, controlling for education(Table F-33).

Table F-33: association of wealth quintile with severe problems obtaining help and advice, by education level

Education level	Log OR	OR for the effect of wealth on difficulty obtaining help/advice	z	p	95% CI of OR
All (unadjusted)	-0.173	0.84	-2.49	0.013	0.73-0.96
None	-0.395	0.67	-0.87	0.386	0.28-1.64
Primary	-0.017	0.98	-0.16	0.876	0.80-1.21
Secondary	-0.156	0.86	-1.17	0.241	0.66-1.11
Diploma+	-0.008	0.99	-0.04	0.972	0.65-1.52

The results in Table F-33 show that within strata, the OR for the effect of a one-step increase in wealth quintile on outcome is no longer statistically significant. A strong effect is only seen in the group with no education, which is the smallest, and is liable to distortion due to the fact that no-one in the group reported low/mild problems. The apparent relationship between wealth and outcome was caused by the fact that people with more education, who have less difficulty receiving help and advice, are also more likely to be financially better off.

The OLR model was fitted using indicator variables for the categorical outcomes, but all three outcomes showed an underlying trend in the ORs and the log likelihood was very little different from an linear model. Therefore the variables were modelled as linear, shown in Table F-34. All three independent variables have a statistically significant association with the odds of problems obtaining help and advice. Limited physical function, a higher level of education, and being in Kenya reduce the odds of problems.

Table F-34: association of physical function, education level and country with severity of problems getting help and advice, using OLR

	Log OR	SE	Z	p	OR	95% CI of OR
Physical function	-0.492	0.160	-3.07	0.002	0.62	0.45-0.84
Education level	-0.620	0.136	-4.54	<0.001	0.54	0.41-0.70
Country	0.973	0.213	4.56	<0.001	2.65	1.74-4.02

F.6.viii Summary of risk factors at baseline

Table F-35 summarises the results of ordinal logistic regression for all seven items. None of the outcomes are associated with CD4 count so it is not included in the table. Physical function is the independent variable most likely to be associated with outcomes, the only exception being difficulty finding life worthwhile. Poor physical function is associated with more pain, symptoms, worry, and difficulty finding peace, but less difficulty sharing feelings or obtaining help and advice. However, the strength of the association is much higher than average for the problems in the physical domain – pain and symptoms. Problems are more common in Uganda for the spiritual and psychosocial domain items (difficulty finding life worthwhile, finding peace, and obtaining help and advice), although not for ability to share feelings.

Wealthier people have a lower probability of pain, symptoms and problems finding life worthwhile, but the effect is not as great for pain as for the other two. More educated people have much better odds of getting help and advice, but education is not associated with any other outcomes. Women worry more and have more difficulty sharing their feelings. Older age increases the probability of finding peace and worth in life, Age was the only independent variable to have a non-linear association with an outcome, in the case where people over 40 have a lower prevalence of problems feeling at peace compared to the baseline of 18-25 year olds, but the 26-40 age group was not affected. Being aged above 25 helps patients find life worthwhile but only being aged over 40 helps them feel at peace.

Some patterns between outcomes are evidence in the table. Pain and symptoms are very similar to each other, both more common for poorer and physically limited people, with similar odds ratios for each, 0.79 and 0.86 for wealth quintile, 3.19 and 3.15 for function. Worry and difficulty sharing feelings also form a pair, except that their relationship with physical function is reversed. Both are more common for women but limited physical function increases worry and reduces difficulty sharing feelings. The other three outcomes are distinct from each other. Each has a unique combination of covariates, but all three are more severe in Uganda than Kenya.

Table F-35: summary of findings from ordinal logistic regression models

	Gender		**Age**		**Education**		**Wealth quintile**		**Physical function**		**Country**	
Reference group	***Male***		***18-25***		***No education***		***Lowest***		***Best***		***Kenya***	
	OR	p	OR	p	OR	p	OR	p	OR	p	OR	p
Pain							0.79 (0.69-0.91)	0.001	3.19 (2.30-4.43)	<0.001		
Symptoms							0.86 (0.75-1.00)	0.046	3.15 (2.26-4.41)	<0.001		
Worry	1.62 (1.10-2.37)	0.014							1.56 (1.16-2.11)	0.004		
Sharing feelings	1.75 (1.21-2.53)	0.003							0.51 (0.38-0.69)	<0.001		
Life worthwhile			0.66 (0.47-0.92)	0.014			0.78 (0.68-0.90)	0.001			2.10 (1.41-3.12)	<0.001
Peace			*[a]1.08* *[b]0.30 (0.16-0.58)*	*0.736* *<0.001*					1.70 (1.27-2.28)	<0.001	2.31 (1.60-3.34)	<0.001
Help and advice					0.54 (0.41-0.70)	<0.001			0.62 (0.45-0.84)	0.002	2.65 (1.75-4.02)	<0.001

[a] compared to age 26-40 [b] compared to age 41-59

F.7 Part C: Change in multidimensional problems over time

F.7.i Recoding continuous time into monthly intervals

As described in the methods, interviews were coded according to the number of days which had passed since recruitment (M0). The first three months were the period of analysis, as specified in the objectives. Table F-36 below shows the number of interviews coded to each time. Interviews which took place outside the specified intervals (e.g. between 38 and 52 days after M0) were excluded. All 438 participants completed an interview on the day of recruitment, and 299 completed an interview between 23 and 37 days later (30 days plus or minus seven). Two hundred and fifty-nine completed an interview 30 days after that, and 232 completed an interview between 83 and 97 days after recruitment.

Table F-36: interviews by time period

	Time period (days from M0)	Interviews
M0	0	438
M1	23 to 37	299
M2	53 to 67	259
M3	83 to 97	232
Retained		1259
Excluded		*296*
Total		1524

Not all participants who completed an interview at M2 also contributed data at M1. There was interim missing data as well as loss to follow-up. The patterns of data collection are shown in Table F-37. Of the 438 participants, 185 completed four interviews at exact monthly intervals within an allowance of seven days. Some participants missed M1(n=16), M2(12) or both(19), and some were lost to follow-up after M2(46), after M1(56) or after M0 (92). Twelve participants missed M1, returned for M2 and then missed M3.

Table F-37: interview completion patterns

	Completed interview				Number of
	M0	M1	M2	M3	participants
	Y	Y	Y	Y	185
	Y	Y	Y		46
	Y	Y		Y	12
	Y	Y			56
	Y		Y	Y	16
	Y		Y		12
	Y			Y	19
	Y				92
Total					438

F.7.ii Missing data

The mean total POS score by month, with 95% confidence intervals, was calculated separately for each group of participants who shared a missingness pattern (Table F-38). Missingness pattern refers to the sequence of observations that were completed. For example, the pattern ‘01-3’ means the participant completed interviews at M0, M1 and M3, but missed M2. The table shows that total POS score was generally higher at M0 for participants who later had missing data than for the 185 participants who completed all four observations at monthly intervals. However, the 95% confidence intervals of the mean total POS score for all the groups that had missing data incorporated the mean score for the group with full data.

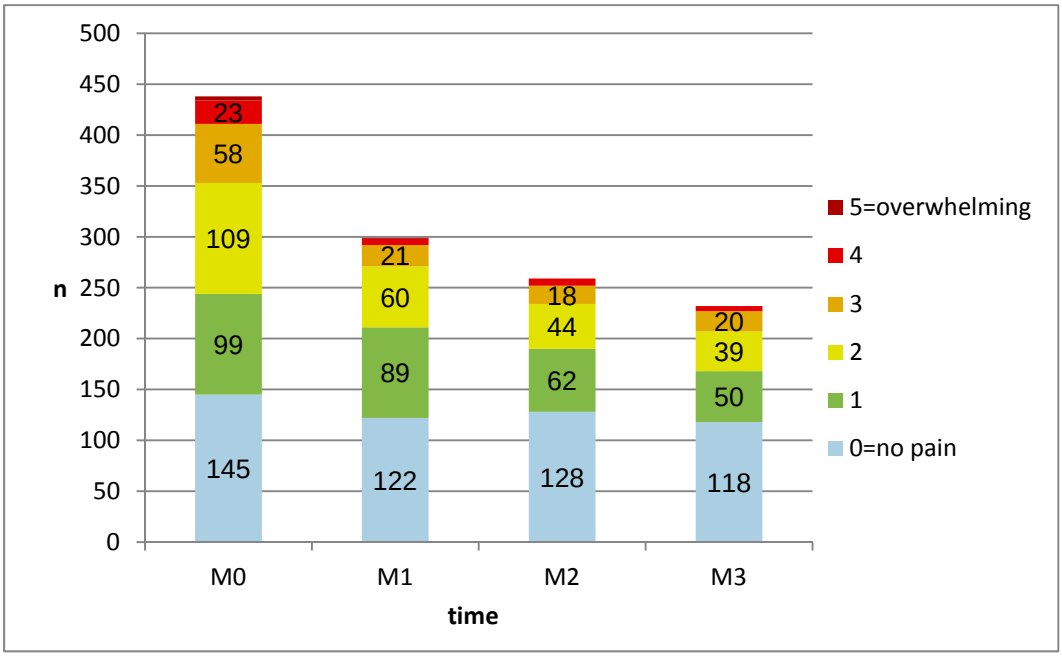
Table F-38: mean total POS score by missingness pattern

		Mean total POS score (95% CI)			
Pattern	N	M0	M1	M2	M3
0123	185	13.62 (12.85-14.39)	11.10 (10.42-11.78)	10.03 (9.32-10.74)	9.56 (8.79-10.34)
012-	46	14.35 (13.00-15.71)	11.46 (10.17-12.74)	9.61 (8.31-10.91)	-
01-3	12	16.0 (13.11-18.89)	14.17 (9.76-18.58)	-	10.58 (7.36-13.81)
01--	56	14.82 (13.38-16.27)	11.75 (10.23-13.27)	-	-
0-23	16	13.81 (11.19-16.44)	-	9.5 (6.96-12.04)	11.13 (8.91-13.34)
0-2-	12	13.50 (11.10-15.90)	-	11.75 (8.43-15.07)	-
0--3	19	15.84 (13.11-18.57)	-	-	11.16 (8.35-13.97)
0---	92	14.47 (13.45-15.31)	-	-	-
Total	438				

F.7.iii POS scores at each time point

Score distributions were plotted by month as stacked bar charts for each POS item in turn. The number of participants is represented, rather than the percentage, and this number is displayed as a label for all values greater than ten.

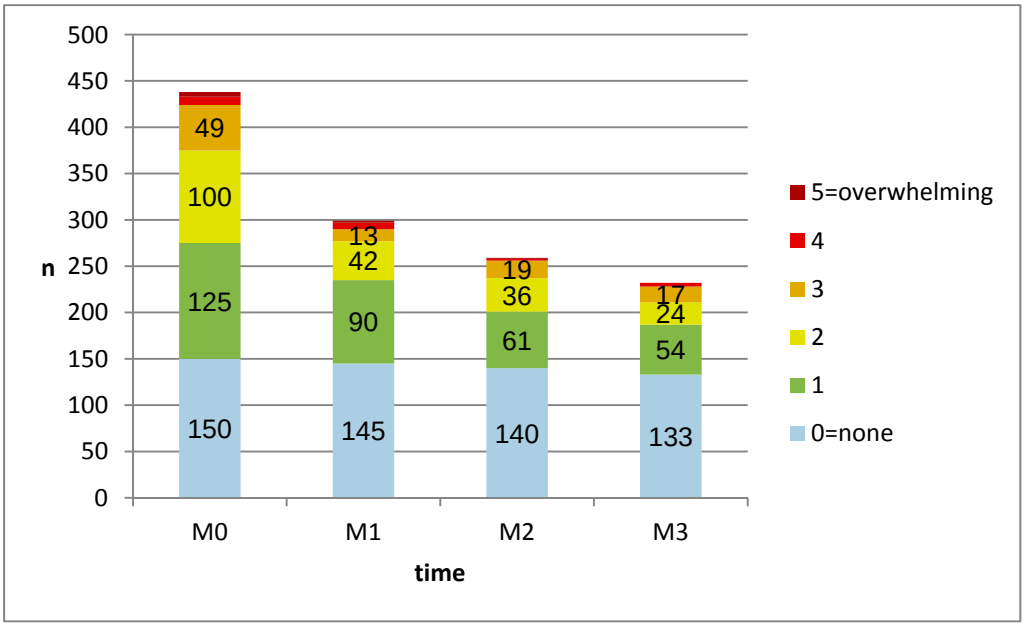
Figure F-7: please rate your pain in the past three days



Score distributions were plotted by month as stacked bar charts for each POS item in turn. The number of participants is represented, rather than the percentage, and this number is displayed as a label for all values greater than ten.

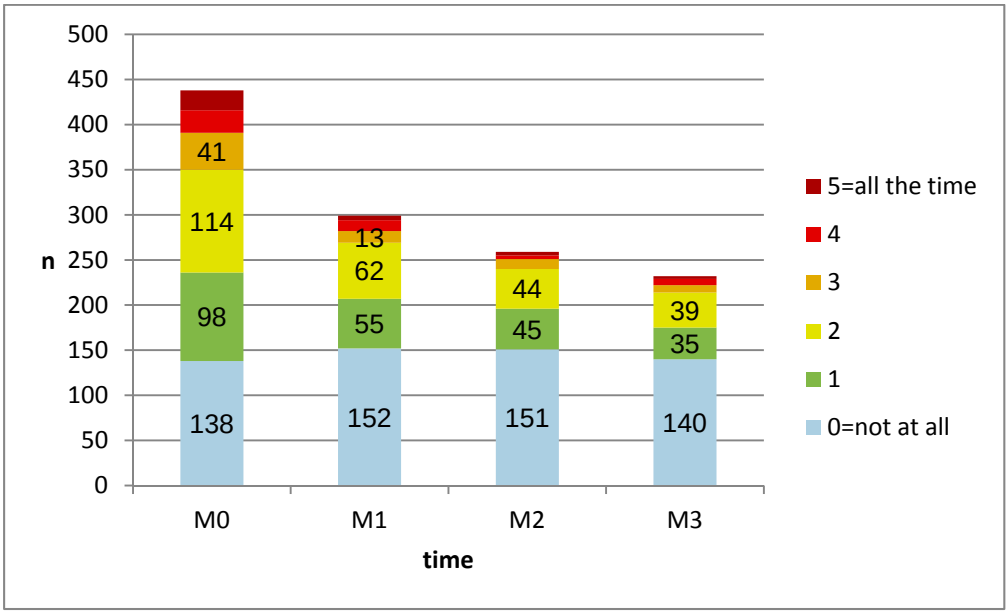
Figure F-7Figure F-7 above shows that the number of people reporting no pain (in blue) decreases slightly over time, from 145 to 118. However, the size of this group proportional to the total increases, because the sample size decreases from 438 at M0 to 232 at M3. A possible explanation for these results would be that participants who report more severe pain at M0 are more likely to be lost to follow-up. This bias could cause a perceived improvement over time when in fact the experience of individuals had not changed. Distinguishing between a sample-level improvement due to responder bias and a genuine individual-level improvement in scores can only be done using longitudinal analysis, in Part D.

Figure F-8: have any other symptoms been affecting how you felt?



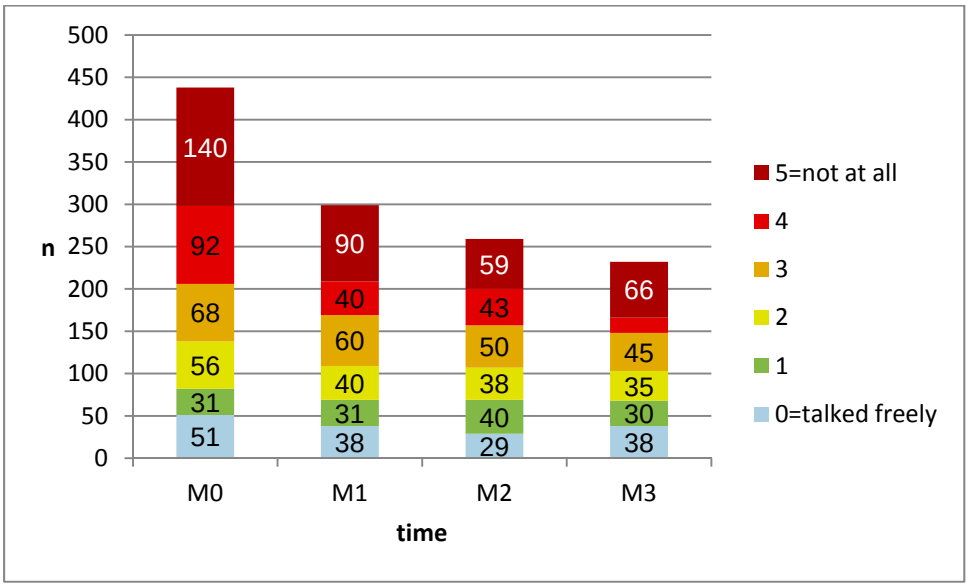
In Figure F-8 above, the distribution of scores over time is similar to the previous figure. The number of people reporting the most severe problems reduces while the number reporting no problems remains almost the same, from 150 to 133.

Figure F-9: have you been feeling worried about your illness?



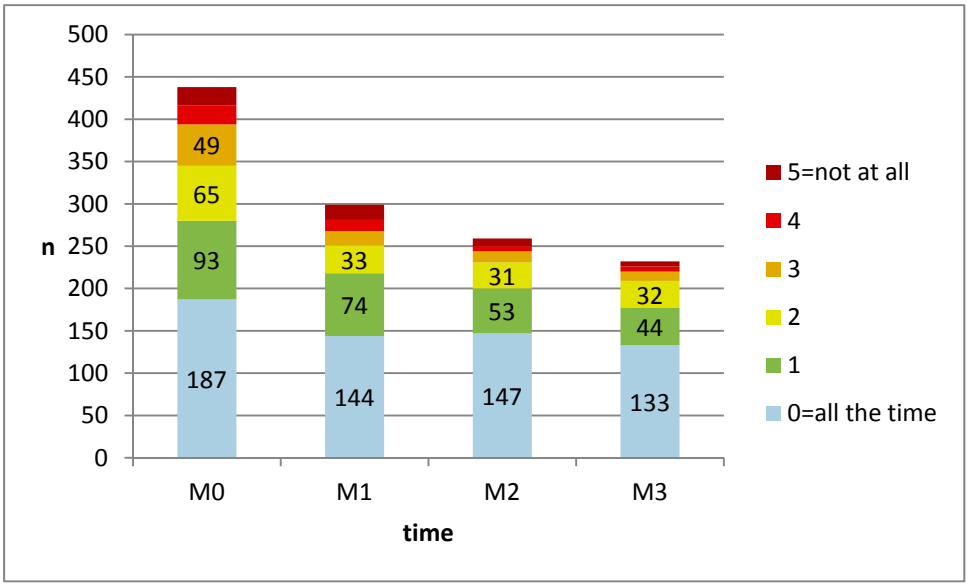
In Figure F-9, the number reporting no worries remains relatively constant at around 150 while the sample size decreases. Scores 3, 4 and 5 reduce, but the number who report score 2 scarcely changes after M2.

Figure F-10: have you been able to share how you are feeling with family or friends?



The distribution of responses to the question ‘have you been able to share how you are feeling’ shown in Figure F-10 is entirely different from those for the previous three items. The worst response (not at all) persists throughout the time period, and at M3 28% of participants (n=66) had still been unable to share their feelings at all in the past three days. The proportion reporting no problem is very low and actually decreases over time, from 51 to a low of 29. Nonetheless, overall scores improve continually.

Figure F-11: have you felt that life was worthwhile?



The distribution of scores for finding life worthwhile (Figure F-11) is more similar to the distributions for the items concerning pain, symptom and worry. One difference is that the number of people reporting that life is worthwhile all the time decreases between M0 and M1, from 187 to 144. It is not possible to tell from the chart whether this was caused by problems increasing or by participants with no problem finding life worthwhile being lost to follow-up.

Figure F-12: have you felt at peace?

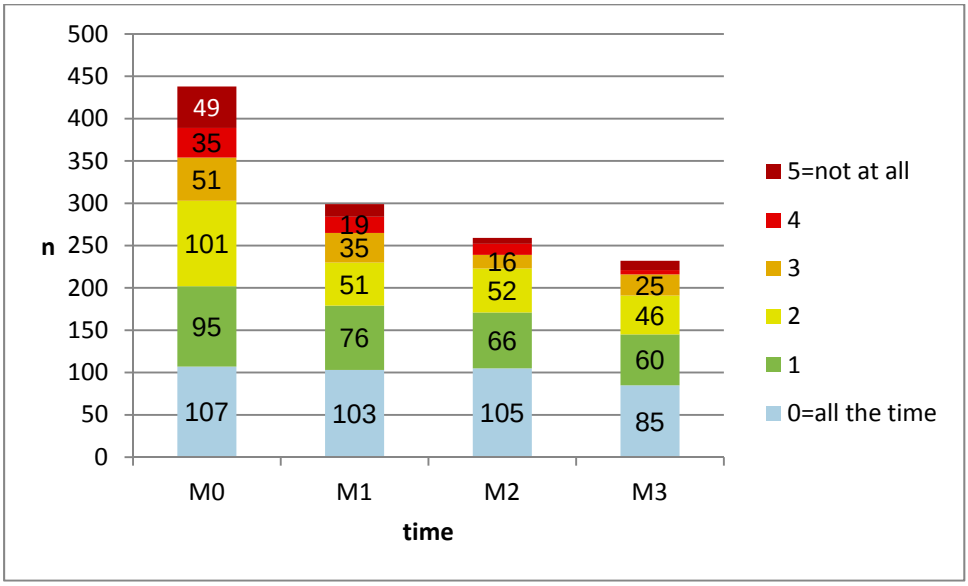
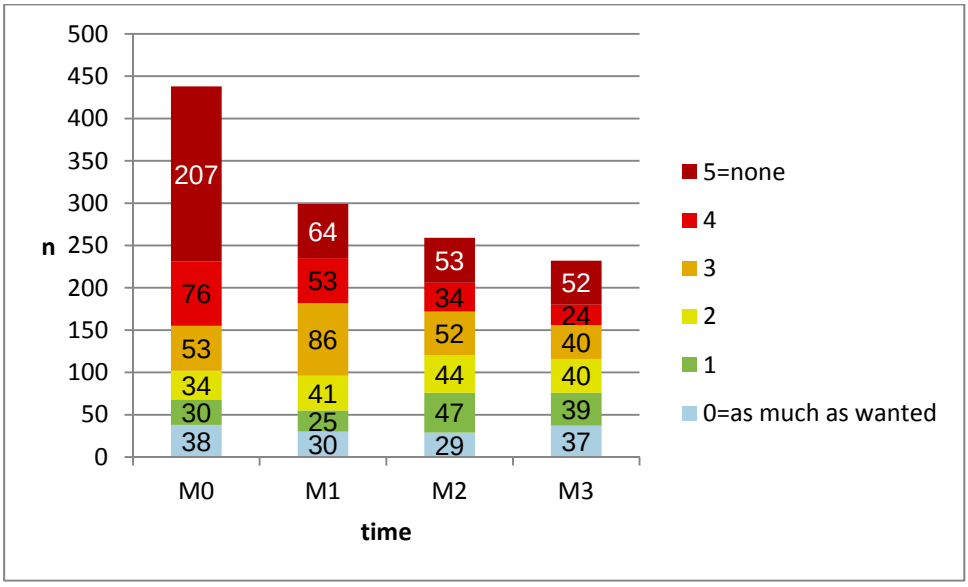


Figure F-12 shows that problems feeling at peace were more prevalent than in several of the other outcomes. The distribution appears similar to Figure F-11, finding life worthwhile, except that scores are suppressed. Feeling at peace all the time is less common than finding life worthwhile all the time at every time point, and the responses 2 and 3 are considerably more common.

Figure F-13: have you had enough help and advice for your family to plan for the future?



The distribution of scores in Figure F-13 is similar to that for the ability to share feelings in Figure F-10. The more severe problems (4 and 5) are highly prevalent, especially at M0. Over time they decrease but the number of people reporting low or moderate problems(0, 1, 2 or 3) does not change markedly.

F.7.iv Total POS score at each time point

The distribution of total POS scores is shown in Table F-39. Over time the mean POS score reduces significantly ($F=56.03$, $p<0.001$ using ANOVA) and after M0 no participants record a total score greater than 29. The proportion recording 15 and over reduces by more than half (47.0% to 21.1%).

Table F-39: total POS score by month

Total POS score	M0	M1	M2	M3
n	*438*	*299*	*259*	*232*
0-4	3.2	7.4	12.0	19.0
5-9	13.7	27.8	35.5	29.3
10-14	36.1	40.1	35.5	30.6
15-19	31.7	17.4	14.3	16.4
20-24	13.2	6.4	2.3	4.3
25-29	1.8	1.0	0.4	0.4
30-35	0.2	0	0	0
Mean	14.2	11.4	10.0	9.9
95% CIs	13.7-14.6	10.8-12.0	9.4-10.6	9.2-10.5
SD	5.0	5.0	4.8	5.3

F.7.v POS score changes over time

Proportion of net change is the number of people whose problem worsened subtracted from the number whose situation improved, expressed as a percentage. It is important to remember throughout this analysis that a high score represents a worse problem, and the optimal POS score for all items is zero.

Table F-40 shows the distribution of change in scores between M0 and M3, for each POS item. In the upper half of the table are the percentage of respondents to report each possible change. For the pain item for example, 0.4% of respondents report that pain is five points lower at M3 than it was at M0, showing the maximum possible improvement on the scale, from a 5 at M0 to a 0 at M3. Meanwhile, 2.2% report that pain has reduced by four points, showing their pain drops either from 5 to 1 or from 4 to 0. Pain score is unchanged for 36.6% of the sample. All results shaded green are an improvement, and results in red are a deterioration.

In the bottom half of the table these results are summarised. The green row represents the total number of people who benefited and the red the total number whose problems got worse. A little under half (43.6%) of participants report that their pain score is lower at M3 than M0; 36.6% report no change, and 19.9% report that it is higher. The net change, the proportion of people whose pain improves minus

those whose pain gets worse, is 43.6-19.9=23.7, within a 95% confidence interval of 20.9 to 26.5. This confidence interval is well above zero, showing a statistically significant net improvement in pain scores over time, after adjusting for response bias.

Table F-40: percentage reporting score change from M0 to M3 (n=232)

Score change	*Pain*	*Symptoms*	*Worry*	*Sharing feelings*	*Life worthwhile*	*Peace*	*Help & advice*
Better by 5	0.4	0.4	3.0	0.4	3.5	3.9	7.3
Better by 4	2.2	1.7	3.0	6.5	3.5	4.3	9.1
Better by 3	7.8	5.2	6.9	8.2	8.6	6.5	12.5
Better by 2	11.2	11.6	17.7	15.1	7.3	9.9	16.0
Better by 1	22.0	28.9	20.3	11.2	12.9	16.8	13.4
The same	36.6	33.6	30.6	28.9	43.1	34.1	22.0
Worse by 1	12.1	13.8	9.5	7.3	13.4	15.1	9.1
Worse by 2	5.2	2.2	6.9	8.6	5.2	3.9	3.9
Worse by 3	2.2	2.6	1.3	9.9	1.3	3.0	3.9
Worse by 4	0.4	0	0.9	2.2	0.4	1.7	2.2
Worse by 5	0	0	0	1.7	0.9	0.9	0.9
Better	43.6	47.8	50.9	41.4	35.8	41.4	58.3
Worse	19.9	18.6	18.6	29.7	21.2	24.6	20.0
Net change	23.7	29.2	32.3	11.7	14.6	16.8	38.3
Standard error	2.8	3.0	3.1	2.1	2.3	2.5	3.2
95% CI	20.9 26.5	26.2 32.2	29.2 35.4	9.6 13.8	12.3 16.9	14.3 19.3	35.1 41.5

As the bottom row of Table F-40 shows, all the confidence intervals are positive, meaning that all seven POS items register a statistically significant net change between M0 and M3. On average, the extent and severity of problems reduces. The biggest improvement is in need for help and advice, and level of worry. These are the two items with the highest prevalence of severe problems at baseline, as shown in Figure F-5.

The table also shows that despite this net improvement during the three-month period, for each item, between 18% and 30% of participants find the problem got worse. The domain in which most people find the problem got worse was in being

able to share their feelings. As a result, this item has the lowest proportion of net change (11.7%).

It is clear that POS item scores improve for all items, in all domains, during the three months of observation for participants who complete interviews at three monthly intervals. A statistically significant change was found for all items over the M0-M3 time period, so the analysis was repeated for the shorter time intervals within this period to establish whether change was steady or fluctuant.

Table F-41: percentage reporting change from M0 to M1 (n=299)

Change	*Pain*	*Symptoms*	*Worry*	*Sharing feelings*	*Life worthwhile*	*Peace*	*Help & advice*
Better by 5	0	0.3	2.3	1.0	3.7	1.7	2.3
Better by 4	2.0	0.3	1.0	4.7	1.7	4.7	3.7
Better by 3	6.7	6.7	5.7	8.4	6.4	7.7	7.4
Better by 2	9.7	11.4	15.4	9.0	6.7	9.7	15.7
Better by 1	21.1	22.4	22.4	13.0	15.1	18.7	21.1
The same	40.8	39.1	34.5	31.4	40.8	35.1	32.8
Worse by 1	9.0	11.4	9.4	13.0	13.4	8.7	8.7
Worse by 2	7.7	7.4	7.7	7.7	4.7	7.7	2.0
Worse by 3	2.7	0.7	0.3	6.7	4.0	3.7	4.0
Worse by 4	0.3	0	0.7	2.3	1.0	1.3	1.7
Worse by 5	0	0.3	0.7	2.7	2.7	1.0	0.7
Better	39.5	41.1	46.8	36.1	33.6	42.5	50.2
Worse	19.7	19.8	18.8	32.4	25.8	22.4	17.1
Net change	19.8	21.3	28.0	3.7	7.8	20.1	33.1
Standard error	2.6	2.7	2.9	1.2	1.8	2.6	3.1
95% CI	17.2 22.4	18.6 24.0	25.1 30.9	2.5 4.9	6.0 9.6	17.5 22.7	30.0 36.2

Problem incidence and severity decrease for all seven items in the month following recruitment (Table F-41), but almost as many people report that sharing their feelings and finding life worthwhile have become more difficult as those who reported benefit. The largest improvement is that over half of people report receiving more help and advice compared to the previous month. Proportion of net change in finding life worthwhile is slight, possibly because the potential for improvement is limited. At

baseline almost half of participants (42.7%) say that they always find life worthwhile (Figure F-5).

Table F-42: percentage reporting change from M1 to M2 (n=231)

Change	*Pain*	*Symptoms*	*Worry*	*Sharing feelings*	*Life worthwhile*	*Peace*	*Help & advice*
Better by 5	0.4	0.4	0.9	1.3	2.6	1.3	0.9
Better by 4	0.4	0.0	0.9	5.6	1.7	0.4	3.5
Better by 3	0.4	1.3	1.3	3.9	3.0	5.6	6.5
Better by 2	8.7	6.9	11.3	9.5	3.9	6.5	14.3
Better by 1	21.2	21.2	17.3	17.3	17.8	16.0	17.8
The same	49.8	45.0	45.9	36.4	49.4	46.8	33.8
Worse by 1	12.6	13.9	9.5	9.5	13.9	14.3	9.5
Worse by 2	5.6	9.1	10.4	7.8	3.5	6.5	7.8
Worse by 3	0.9	1.7	1.3	4.8	2.6	0.9	3.0
Worse by 4	0.0	0.4	0.4	3.0	0.4	0.9	1.7
Worse by 5	0.0	0.0	0.9	0.9	1.3	0.9	1.3
Better	31.1	29.8	31.7	37.6	29.0	29.8	43.0
Worse	19.1	25.1	22.5	26.0	21.7	23.5	23.3
Net change	12.0	4.7	9.2	11.6	7.3	6.3	19.7
Standard error	2.1	1.4	1.9	2.1	1.7	1.6	2.6
95% CI	9.9 14.1	3.3 6.1	7.3 11.1	9.5 13.7	5.6 9.0	4.7 7.9	17.1 22.3

There are 299 participants who completed an interview between 23 days and 37 days after recruitment to the study (which took place up to 14 days after their HIV diagnosis), and 259 completed an interview between 53 and 67 days after recruitment. Scores at the two time points for the 231 who completed interviews at both are compared in Table F-42. For most items, proportion of net change is less than it had been between M0 and M1. The exceptions are for peace, where it remains the same, and finding life worthwhile. On average, there is greater improvement in ability to share feelings during the second month after diagnosis than during the first. The number of people experiencing decreased symptoms is only a little greater than the number whose symptoms worsened. Pain scores do not change a great deal for most people. Half of participants report no change, and of the remaining half, for 68% the increase or reduction in pain is by a single point on the six-point scale.

The largest proportion of net change is for help and advice, where 43% of people report more help and advice than the previous month as compared to 23% who report less. The table shows that about a third of people report no change and another third report a score either one or two points lower than at M1.

Compared to the preceding month, it is more common to report no change. For five of the seven items, between 45% and 50% of participants report the same score as M2 as at M1. Ability to share feelings and need for help and advice are more likely to alter.

Table F-43: percentage reporting change from M2 to M3 (n=201)

Change	*Pain*	*Symptoms*	*Worry*	*Sharing feelings*	*Life worthwhile*	*Peace*	*Help & advice*
Better by 5	0.0	0.0	1.0	1.5	2.0	0.0	1.0
Better by 4	0.0	0.5	0.5	4.0	0.5	2.0	2.5
Better by 3	2.5	1.0	1.5	6.5	3.0	3.5	5.0
Better by 2	9.0	9.5	8.0	8.5	4.5	6.0	10.0
Better by 1	13.4	16.9	12.9	16.9	10.0	11.0	15.9
The same	48.3	47.3	58.2	32.8	60.7	48.3	39.8
Worse by 1	14.9	16.4	9.5	13.9	9.5	17.9	8.0
Worse by 2	10.5	4.5	6.0	7.0	7.5	5.5	10.5
Worse by 3	0.5	3.5	1.5	2.5	0.5	2.5	5.0
Worse by 4	1.0	0.5	0.5	4.5	1.5	1.0	2.5
Worse by 5	0.0	0.0	0.5	2.0	0.5	2.5	0.0
Better	24.9	27.9	23.9	37.4	20.0	22.5	34.4
Worse	26.9	24.9	18.0	29.9	19.5	29.4	26.0
Net change	-2.0	3.0	5.9	7.5	0.5	-6.9	8.4
Standard error	0.9	1.1	1.5	1.7	0.5	1.8	1.8
95% CI	-2.9 -1.1	1.9 4.1	4.4 7.4	5.8 9.2	0.0 1.0	-8.7 -5.1	6.6 10.2

The change in multidimensional problem severity and prevalence between two months and three months after recruitment is shown in Table F-43. The proportion of net change is lower for all items than in the previous month, except for peace, where the magnitude of change is maintained and the direction reversed. More people have difficulty feeling at peace at M3 than M2.

For most people, problems in the areas of worry or peace do not change in the third month after recruitment. However, problems sharing feelings or getting help and advice are still changing, sometimes by the entire length of the scale. The proportion of net change for worry and ability to share feelings are similar, but there is much total change, both for better and for worse in ability to share feelings. Much of this cancels out, leaving a small overall reduction in problems. The implication of these findings is that problems sharing feelings come and go quickly over time, while worry which is maintained two months after diagnosis is a more fixed trait.

The proportion of net change results for each item over the total three-month period and month by month are summarised in Table F-44. For six of the seven items, the largest proportion of net change occurs in the first month, and for five of the seven there is least change in the third month. The results for ability to share feelings are unique, in that the majority of improvement is delayed until the second and third months following recruitment.

Most pain reduction takes place in the first month after recruitment, with some further gain in the second month followed by a small but significant reversal, as the number of people with pain increases slightly. The majority of symptom amelioration similarly takes place by M1. After this there is only slight increase in the number of people whose symptom burden is reduced, but the reverse in direction of net effect seen with pain never takes place. Worry abates for a large number of people in the first month after recruitment, and a smaller number in the months after M1.

Proportion of net change is low but constant in the first two months after recruitment when patients are asked whether they find life worthwhile. After M2 there is virtually no change. The proportion of people to feel at peace increases in the month up to M1, and improves a little more up to M2, but in the next month this gain is completely reversed. The people who feel less at peace outnumber those who felt more at peace. The largest proportion of net change is seen in the number of people who felt they have enough help and advice. The majority of this gain occurs in the first month, after which improvement steadily declines.

Overall, the patterns of change over time are similar for four outcomes: pain, symptoms, worry, and difficulty accessing help/advice. in all four cases, improvement is rapid at first and reduces over time. Difficulty finding peace behaves similarly, with the difference that net change does not only slow down but reverses direction in the third month as participants have more difficulty finding peace. Difficulty sharing feelings is more fluctuant than other outcomes, and difficulty finding life worthwhile is more stable.

F.7.vi Summary of change over time

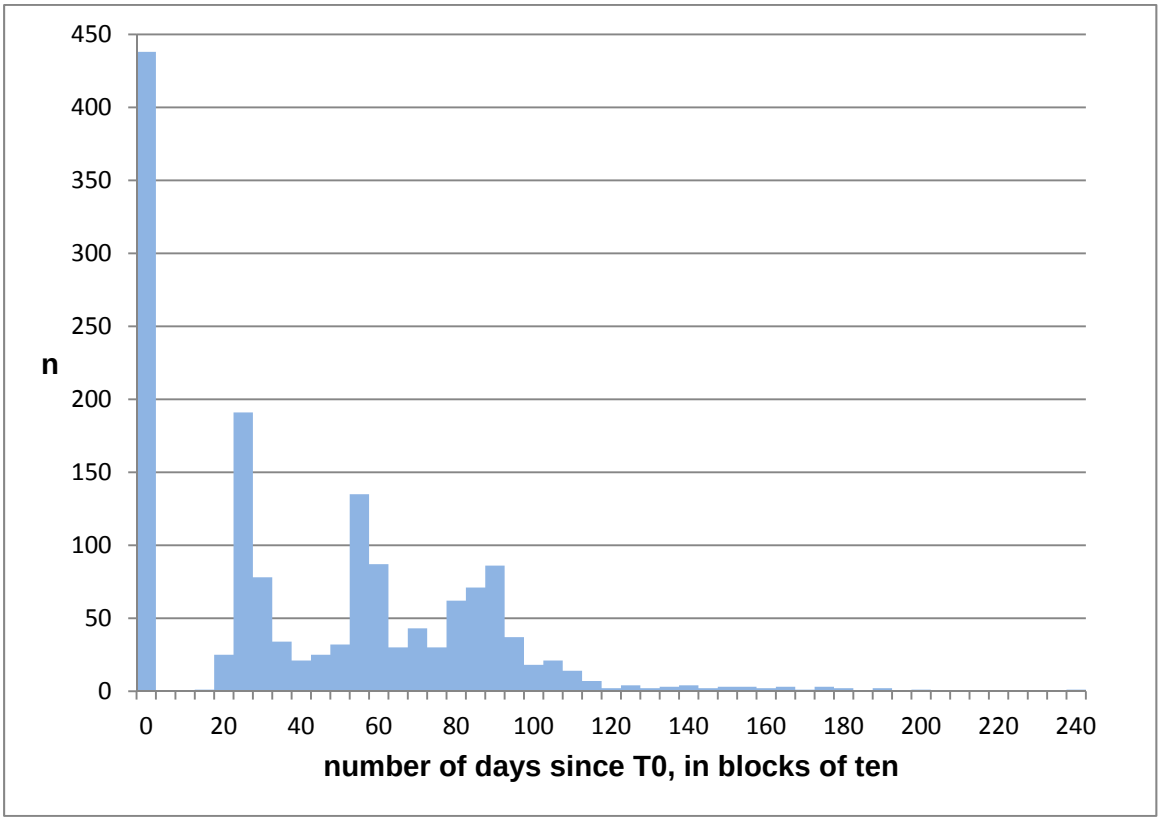
Table F-44: proportion of net change over each time interval

	Pain	Symptoms	Worry	Sharing feelings	Life worthwhile	Peace	Help & advice
	Proportion of net change and 95% CI						
M0 to M3	23.7 (20.9-26.5)	29.2 (26.2-32.2)	32.3 (29.2-35.4)	11.7 (9.6-13.8)	14.6 (12.3-16.9)	16.8 (14.3-19.3)	38.3 (35.1-41.5)
M0 to M1	19.8 (17.2-22.4)	21.3 (18.6-24.0)	28.0 (25.1-30.9)	3.7 (2.5-4.9)	7.8 (6.0-9.6)	20.1 (17.5-22.7)	33.1 (30.0-36.2)
M1 to M2	12.0 (9.9-14.1)	4.7 (3.3-6.1)	9.2 (7.3-11.1)	11.6 (9.5-13.7)	7.3 (5.6-9.0)	6.3 (4.7-7.9)	19.7 (17.1-22.3)
M2 to M3	-2.0 (-2.9 to -1.1)	3.0 (1.9-4.1)	5.9 (4.4-7.4)	7.5 (5.8-9.2)	0.5 (0.0-1.0)	-6.9 (-8.7 to -5.1)	8.4 (6.6-10.2)

F.8 Part D: Risk factors for multidimensional problems over time

Because time to an event usually follows a Poisson distribution, with a tail to the right, the analysis plan stated that outliers (observations that occurred more than three standard deviations from the mean) would be excluded. The mean number of days from T0 to interview completion is 45.3 (standard deviation 39.1) so the point three standard deviations above the mean is 162.6. Figure F-14 below shows the number of days from T0 to data collection for all observations. As expected, it is constrained on the left with a long tail to the right. The four successive peaks, decreasing in size, show the effect of a fixed monthly pattern. Over time the sample size decreases and random variation increases. Thirteen data points were completed more than 162 days after T0 (maximum 242), and these were excluded as planned, leaving 1511 observations of which 438 are at T0 and 1073 are follow-up observations. A complete dataset would have had 438 x 4 = 1752 observations, so missingness was 13.8%.

Figure F-14: histogram of number of days from recruitment to observations



F.8.i Pain

The following analysis identifies risk factors for prevalence of pain (defined as a pain score of 2, 3, 4 or 5) over time.

Table F-45: results of population averaged logit models fitting one variable at a time to pain prevalence

	Log OR	SE	Z	p	OR	95% CI of OR	Carried forward
Gender	-0.082	0.145	-0.57	0.569	0.92	0.69-1.22	No
Age	0.161	0.116	1.39	0.166	1.17	0.94-1.48	Yes
Wealth quintile	-0.245	0.050	-4.85	<0.001	0.78	0.70-0.86	Yes
Education	-0.120	0.096	-1.25	0.210	0.89	0.73-1.07	Yes
Physical function	1.067	0.110	9.66	<0.001	2.91	2.34-3.61	Yes
Country	0.178	0.141	1.26	0.207	1.19	0.91-1.57	Yes
ART use	-0.059	0.128	-0.46	0.645	0.94	0.73-1.21	No
Time from T0	-0.011	0.001	-7.25	<0.001			

Of the seven independent variables apart from time, five were associated with prevalence of pain at 25% significance(Table F-45). These consisted of two variables with a less than 0.1% probability of occurring by chance (namely, physical function and wealth quintile) and three with a greater than 10% probability of association by chance (age, education and country). Physical function had the OR furthest from 1, indicating the strongest association.

Physical function and wealth quintile, which were the most convincingly associated with pain prevalence in multivariate analysis, were the only two variables to retain an association at the 5% level in a multivariate model. There was weak evidence of older age predicting pain, with the 95% confidence intervals just crossing one, while education and country no longer showed an effect on pain prevalence. In accordance with the downward stepwise method, education (which had the highest p-value) was removed and a model was fitted using the remaining covariates Country was still non-significant so it was removed next. Age was now weakly associated with the outcome (OR=1.26) with low significance (p=0.056). The removal of age as a covariate made very little difference to the other elements of the model, apart from reducing the constant. The fact that other parameters did not alter suggests that the association between age and pain prevalence, while only weakly significant, was independent of other variables.

Table F-46: results of population-averaged multivariate logit model of pain prevalence

	Log OR	SE	Z	p	OR	95% CI of OR
Days since T0	-0.010	0.002	-6.42	<0.001	0.99	0.99-0.99
Wealth quintile	-0.217	0.052	-4.17	<0.001	0.81	0.73-0.89
Physical function	1.039	0.111	9.33	<0.001	2.83	2.27-3.52
Constant	-0.121	0.181	-0.67	0.506		

In the final model in Table F-46, time appears to have very little effect, with an OR of 0.99. However, it must be remembered that this is the effect on pain prevalence of a single day. Over the 163 days of observation in the model, the effect of time was substantial, as shown graphically in Figure F-15 where the fitted odds of pain over time are presented. Darker shades of blue indicate more wealth.

Figure F-15: predicted response curves for the model in Table F-46

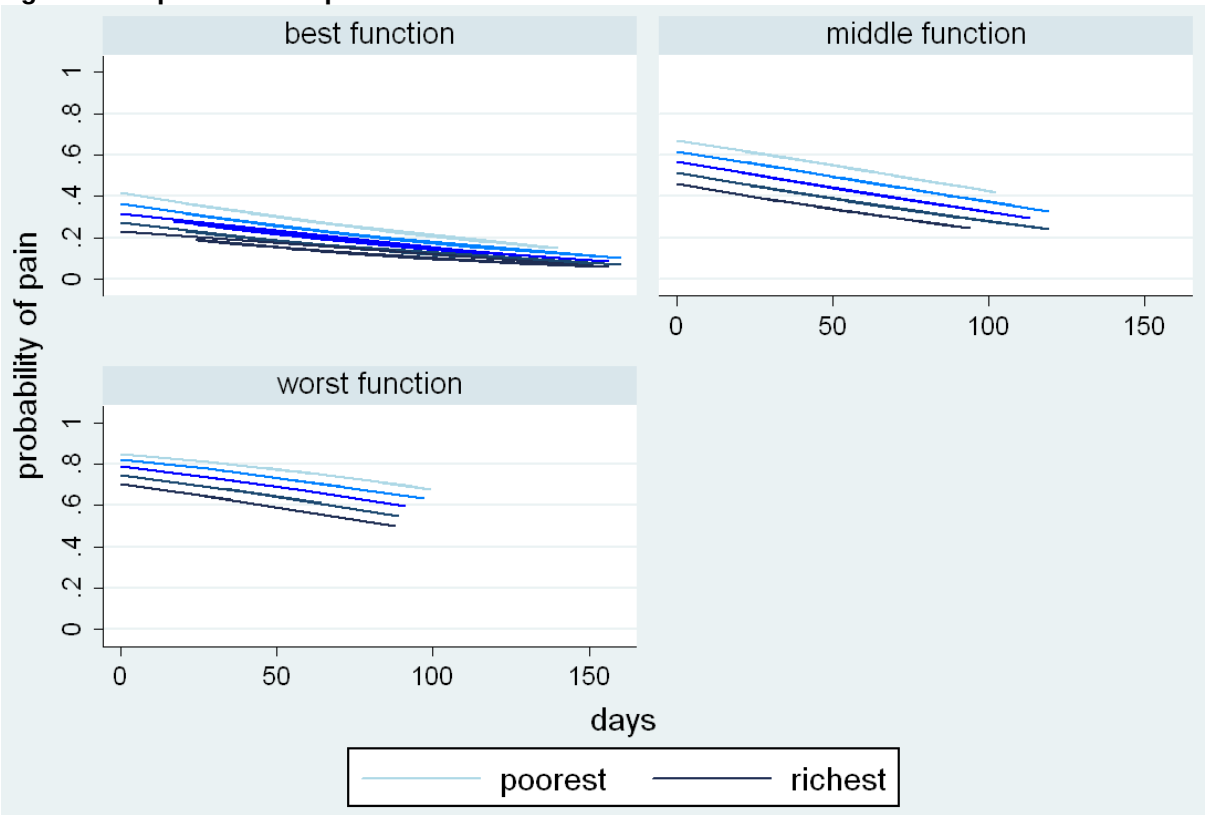


Figure F-15 shows that wealth quintile is associated with reduced probability of pain, at all times, but the effect of physical function is larger. The prevalence of pain is high and only those with the best function achieve probability below 20% in three months. It is noticeable that the curves for those with middle physical function are

shorter. This is because no participants in this group completed interviews more than 120 days after recruitment.

These graphs, and the others used in this section, are used only as a visual representation of the model. The graph lines do not trace the probability of an individual having a certain problem. They are averaged on a log scale rather than an ordinal scale, therefore they cannot be converted back into simple probabilities.

F.8.ii Symptoms

Table F-47: results of population averaged logit models fitting one variable at a time to symptom prevalence

	Log OR	SE	Z	p	OR	95% CI of OR	Carried forward
Gender	-0.151	0.150	-1.01	0.313	0.86	0.64-1.15	No
Age	0.184	0.121	1.51	0.130	1.20	0.95-1.52	Yes
Wealth quintile	-0.137	0.052	-2.62	0.009	0.87	0.79-0.97	Yes
Education	-0.112	0.100	-1.12	0.263	0.89	0.73-1.09	No
Physical function	1.116	0.112	9.96	<0.001	3.05	2.45-3.80	Yes
Country	0.402	0.146	2.75	0.006	1.49	1.12-1.99	Yes
ART use	-0.191	0.139	-1.37	0.172	0.83	0.63-1.09	Yes
Time from T0	-0.011	0.002	-6.89	<0.001			

Five covariates (age, wealth quintile, physical function, country and ART use) were significant at the 25% level in Table F-47. Physical function had the strongest association. Most associations were weak, with ORs of 0.83-0.89. A population-averaged logistic regression model was fitted to the probability of symptoms over time.

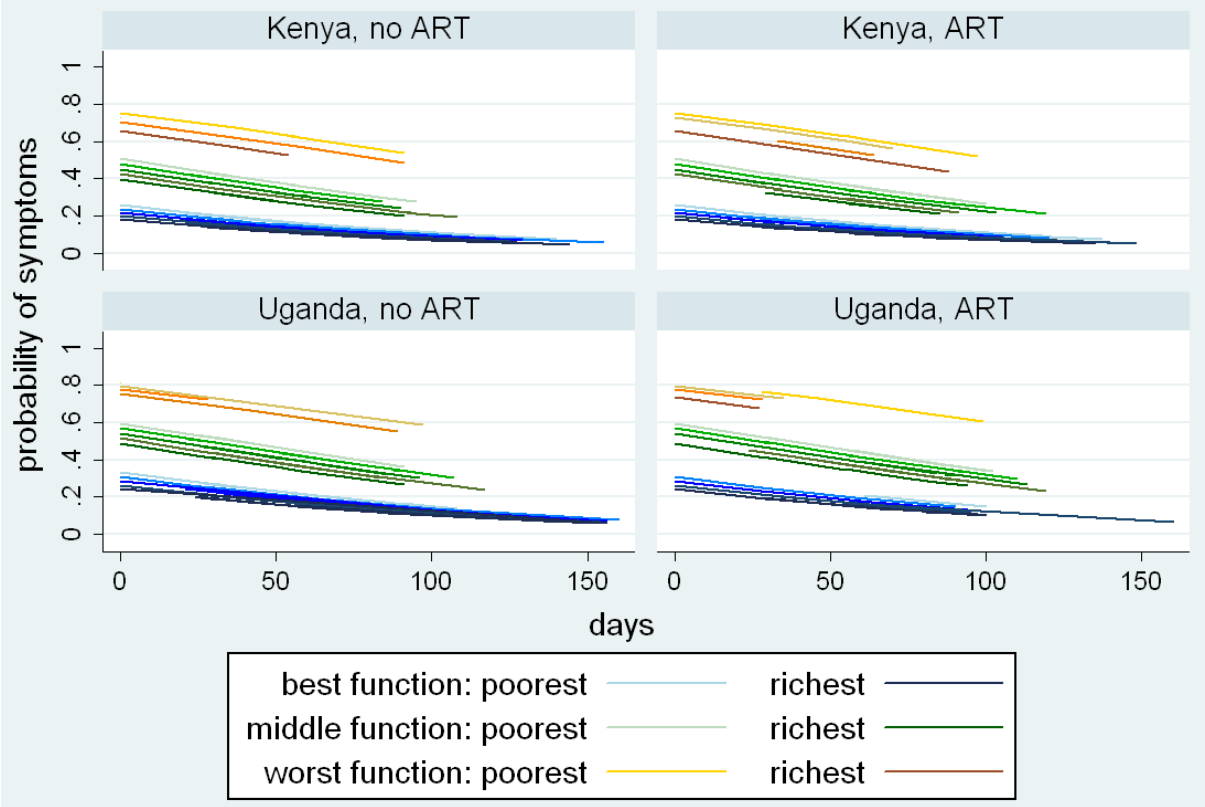
Age and country, which had the weakest association with the outcome in bivariate analysis in Table F-47, continued to have a weaker association in the fitted model. Country had an OR of 1.35 and p-value of 0.052, just outside significance. After the removal of age, the effect of country became statistically significant, with the p-value changing to 0.049 (Table F-48), so it was retained in the model.

Table F-48: results of population-averaged multivariate logit model of symptom prevalence

	Log OR	SE	Z	p	OR	95% CI of OR
Days since T0	-0.009	0.002	-5.27	<0.001	0.99	0.99-0.99
Wealth quintile	-0.114	0.055	-2.07	0.039	0.89	0.80-0.99
Physical function	1.129	0.115	9.79	<0.001	3.09	2.47-3.88
Country	0.306	0.156	1.97	0.049	1.36	1.00-1.84
ART use	-0.380	0.152	-2.50	0.013	0.68	0.51-0.92
Constant	-1.159	0.286	-4.05	<0.001		

Table F-48 shows that the odds of symptoms reduced over time, and that poverty, physical impairment and living in Uganda were associated with higher symptom prevalence. Of these, physical function made the most difference, tripling the odds of symptoms for every increase. Also, participants who took ART had a lower symptom prevalence than those who did not. Figure F-16 shows the fitted curves from the model in Table F-48.

Figure F-16: predict response curves for the model in Table F-48



The blue lines represent the population average probability of symptoms over time for those with the best physical function. The green lines show the populations with middle physical function and the orange those with the worst. Within each colour, the lines shade from the highest quintile in the darkest shade to the lowest quintile in the

lightest. Populations from the two countries are graphed separately, and those taking ART are also separated out.

It is clear that physical function is the covariate with the largest effect on symptom prevalence. The differences between the two countries and between the ART and non-ART populations are relatively minor in comparison.

Only 30 people in the sample of 438 were recorded in the worst category of physical fucniton (ECOG score 2, 3 or 4). In this model, the 30 patients have been subdivided by five wealth quintiles, two countries and two treatment options, giving 20 groups. Some of these groups did not contain a single patient, which is the reason why only two or three lines in orange appear on each graph above, rather than the maximum five.

F.8.iii Worry

Table F-49: results of population-averaged logit models fitting one variable at a time to worry prevalence

	Log OR	SE	Z	p	OR	95% CI of OR	Carried forward
Gender	0.245	0.144	1.70	0.089	1.28	0.96-1.69	Yes
Age	0.018	0.113	0.16	0.876	1.02	0.81-1.27	No
Wealth quintile	-0.044	0.048	-0.92	0.359	0.96	0.90-1.05	No
Education	0.101	0.093	1.09	0.276	1.11	0.92-1.33	No
Physical function	0.468	0.104	4.50	<0.001	1.60	1.30-1.96	Yes
Country	0.501	0.137	3.66	<0.001	1.65	1.26-2.16	Yes
ART use	-0.227	0.129	-1.76	0.078	0.80	0.62-1.03	Yes
Time from T0	-0.012	0.001	-7.82	<0.001			

Four covariates (gender, physical function, country and ART use) were significant at the 25% level in bivariate analysis in Table F-49. They were carried forward into a population-averaged logistic regression model was fitted to the probability of symptoms over time. ART use, which had good significance but a weak OR in bivariate analysis, was no longer significantly associated with the odds of worry in multivariate analysis, so it was removed and a new model was fitted.

Table F-50: results of population-averaged multivariate logit model of worry prevalence

	Log OR	SE	Z	p	OR	95% CI of OR
Days since T0	-0.011	0.002	-7.55	<0.001	0.99	0.99-0.99
Gender	0.295	0.146	2.03	0.043	1.34	1.01-1.79
Physical function	0.454	0.105	4.31	<0.001	1.57	1.28-1.94
Country	0.467	0.139	3.35	0.001	1.60	1.21-2.10
Constant	-1.307	0.244	-5.35	<0.001		

In this new model, three covariates are associated with the outcome at p<0.05(Table F-50). The probability of worry decreases over time. Women, people in Uganda, and people with impaired physical function have higher odds of worry, but the ORs are not very high for any variable.

Figure F-17: predicted response curves for the model in Table F-50

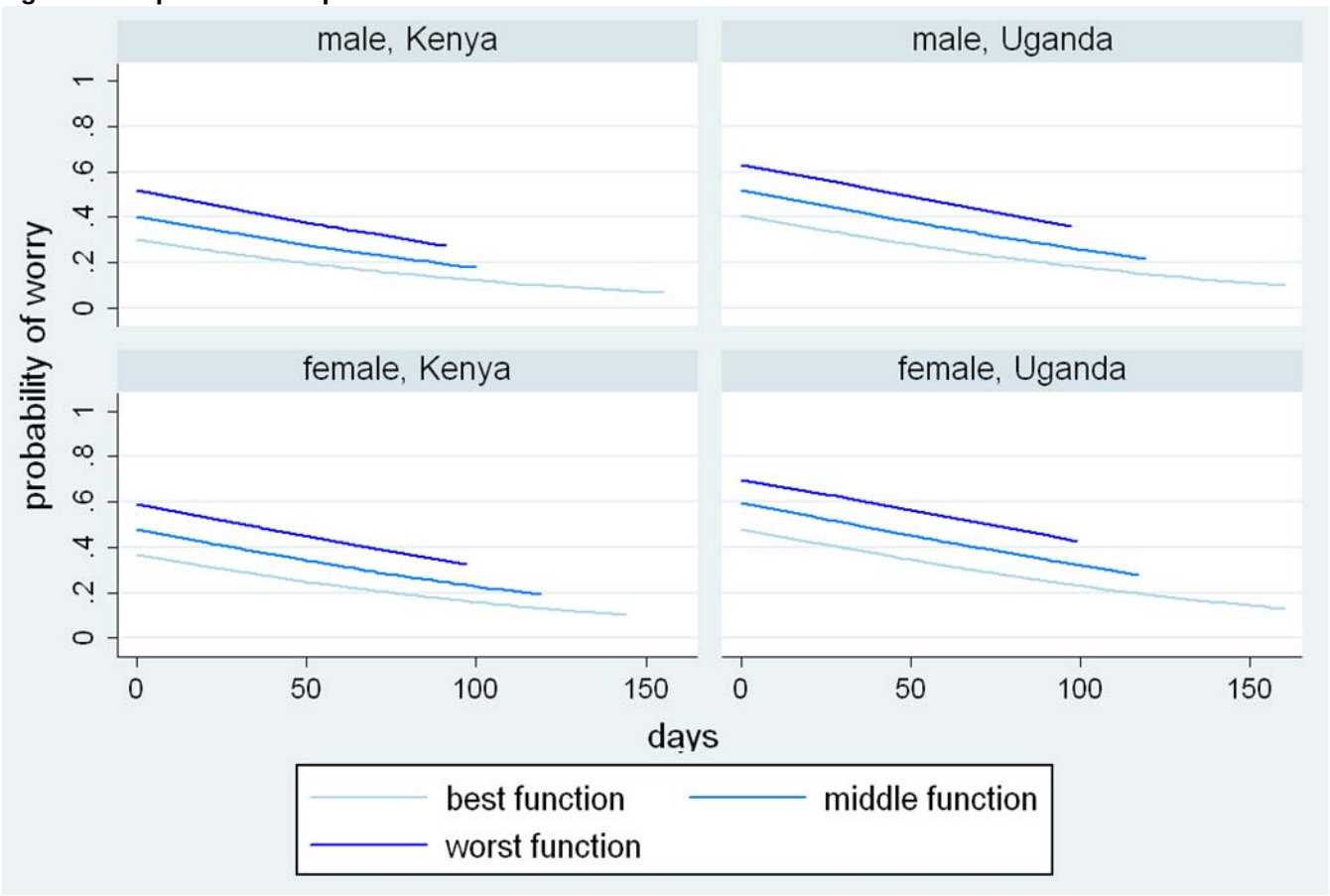


Figure F-17 shows the predicted results from the model in Table F-50. The graphs show that the probability of worry decreases over time. The curve begins to flatten out after about 100 days, seen most clearly in the group with best physical function. Being female, living in Uganda, or having restricted function all have a similar effect

on the probability of worry, also shown by the fact that ORs for gender, country and function in Table F-50 are similar.

F.8.iv Difficulty sharing feelings

Table F-51: results of population-averaged logit models fitting one variable at a time to prevalence of difficulty sharing feelings

	Log OR	SE	Z	p	OR	95% CI of OR	Carried forward
Gender	0.213	0.150	1.42	0.155	1.24	0.93-1.66	Yes
Age	-0.146	0.121	-1.20	0.230	0.86	0.68-1.10	Yes
Wealth quintile	0.157	0.052	3.01	0.003	1.17	1.06-1.30	Yes
Education	-0.101	0.099	-1.02	0.308	0.90	0.75-1.10	No
Physical function	-0.387	0.111	-3.49	<0.001	0.68	0.55-0.84	Yes
Country	-0.167	0.147	-1.14	0.256	0.85	0.63-1.13	No
ART use	0.030	0.136	0.22	0.827	1.03	0.79-1.35	No
Time from T0	-0.005	0.002	-2.99	0.003			

When analysed individually, four variables were associated with difficulty sharing feelings at 25% significance(Table F-51). These were gender, age and wealth quintile (weak associations) and physical function, with a slightly stronger association (OR=0.68) that was highly significant (p<0.001).

In a multivariate model using these four variables plus time, gender was the covariate with the largest p-value above 0.05 (OR=1.17, p=0.304), so it was removed. Refitted without gender, age became fractionally more closely associated with the outcome, although the OR did not move outside the previous confidence intervals. However, age was still not significant at the 5% level, so it was removed.

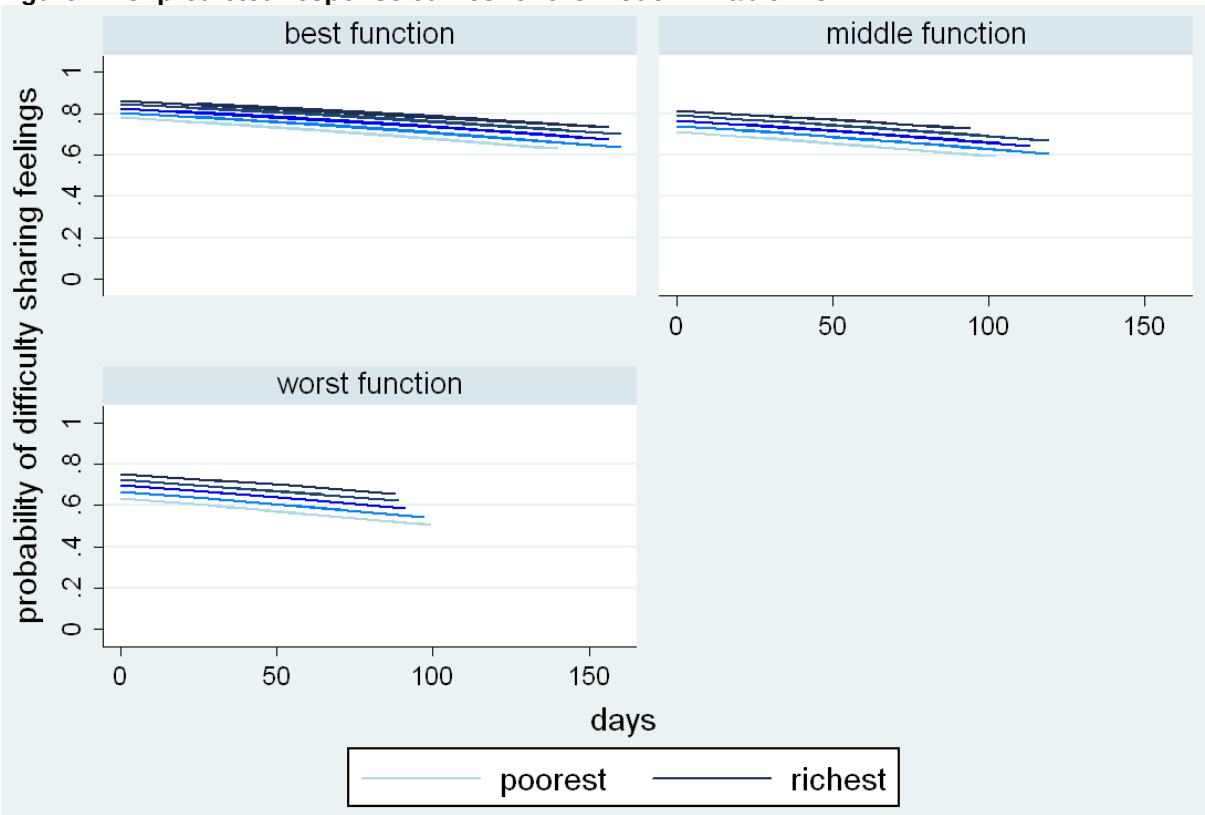
Table F-52: results of population-averaged multivariate logit model of prevalence of problem sharing feelings

	Log OR	SE	Z	p	OR	95% CI of OR
Days since T0	-0.005	0.002	-3.39	0.001	1.00	0.99-1.00
Wealth quintile	0.141	0.052	2.71	0.007	1.15	1.04-1.27
Physical function	-0.365	0.111	-3.27	0.001	0.69	0.56-0.86

Table F-52 shows that difficulty sharing feelings became less prevalent over time, and was more likely for those with impaired physical function and for the wealthier

participants. None of these effects were particularly strong. The effect of time in days was indistinguishable from zero (that is, an OR of 1) to two decimal places.

Figure F-18: predicted response curves for the model in Table F-52



The consequences of the small effects in Table F-68 are shown graphically in Figure F-18. The slope is shallow compared to the graphs of other outcomes, showing that being able to share feelings remained a problem throughout the observation period. Even the group with the lowest probability of problems in this area (which was the poorest quintile with the worst physical function) still had a 50% probability of difficulty sharing feelings over three months after diagnosis, according to the fitted prediction.

F.8.v Difficulty finding life worthwhile

Table F-53: results of population-averaged logit models fitting one variable at a time to prevalence of problem feeling life worthwhile

	Log OR	SE	Z	p	OR	95% CI of OR	Carried forward
Gender	0.146	0.161	0.91	0.364	1.16	0.84-1.59	No
Age	-0.411	0.129	-3.18	0.001	0.66	0.51-0.85	Yes
Wealth quintile	-0.221	0.055	-4.02	<0.001	0.80	0.72-0.89	Yes
Education	-0.159	0.106	-1.50	0.134	0.85	0.69-1.05	Yes
Physical function	0.574	0.106	5.43	<0.001	1.78	1.44-2.19	Yes
Country	0.962	0.153	6.29	<0.001	2.62	1.94-3.53	Yes
ART use	-0.274	0.135	-2.03	0.043	0.76	0.58-0.99	Yes
Time from T0	-0.007	0.001	-4.58	<0.001			

All covariates apart from gender were associated with the probability of difficulty finding life worthwhile, so they were carried forward into a multivariate model. In multivariate analysis, education was no longer associated with finding life worthwhile (OR=0.94, p=0.604), so it was dropped. Without education, the significance of ART crossed the significance threshold (p=0.054), but the OR was substantially different from one (0.75), suggesting a real effect. Wealth quintile, with an OR closer to one (OR=0.78), had a much lower p-value (p<0.001), probably because it has more degrees of freedom which makes the same result less probable due to chance. Following the analysis plan in which 5% significance was required for inclusion, ART was removed, as shown in Table F-54.

Table F-54: results of population-averaged multivariate logit model of prevalence of problem feeling life worthwhile

	Log OR	SE	Z	p	OR	95% CI of OR
Days since T0	-0.007	0.002	-4.71	<0.001	0.99	0.99-1.00
Age	-0.398	0.126	-3.16	0.002	0.67	0.52-0.86
Wealth quintile	-0.253	0.056	-4.48	<0.001	0.78	0.70-0.87
Physical function	0.488	0.111	4.39	<0.001	1.63	1.31-2.02
Country	1.042	0.156	6.69	<0.001	2.83	2.09-3.84

Odds of difficulty finding life worthwhile are lower for older people and people in a higher economic quintile, while problems are more likely for those with impaired physical function and for Ugandans. Of these covariates, country makes the most difference (OR=2.83).

This model includes variables with respectively three, five, three and two categories, (age, wealth quintile, physical function, and country) making 90 possible combinations. Therefore the model cannot be represented with graphs in any useful way.

F.8.vi Difficulty finding peace

Table F-55: results of population-averaged logit models fitting one variable at a time to prevalence of problem feeling at peace

	Log OR	SE	Z	p	OR	95% CI of OR	Carried forward
Gender	0.040	0.150	0.27	0.788	1.04	0.78-1.40	No
Age	-0.477	0.123	-3.88	<0.001	0.62	0.49-0.79	Yes
Wealth quintile	-0.022	0.051	-0.42	0.675	0.98	0.88-1.08	No
Education	0.082	0.098	0.83	0.404	1.09	0.90-1.32	No
Physical function	0.646	0.103	6.26	<0.001	1.91	1.56-2.33	Yes
Country	1.090	0.146	7.45	<0.001	2.97	2.23-3.96	Yes
ART use	-0.470	0.112	-3.99	<0.001	0.63	0.50-0.79	Yes
Time from T0	-0.006	0.086	-0.07	0.941			

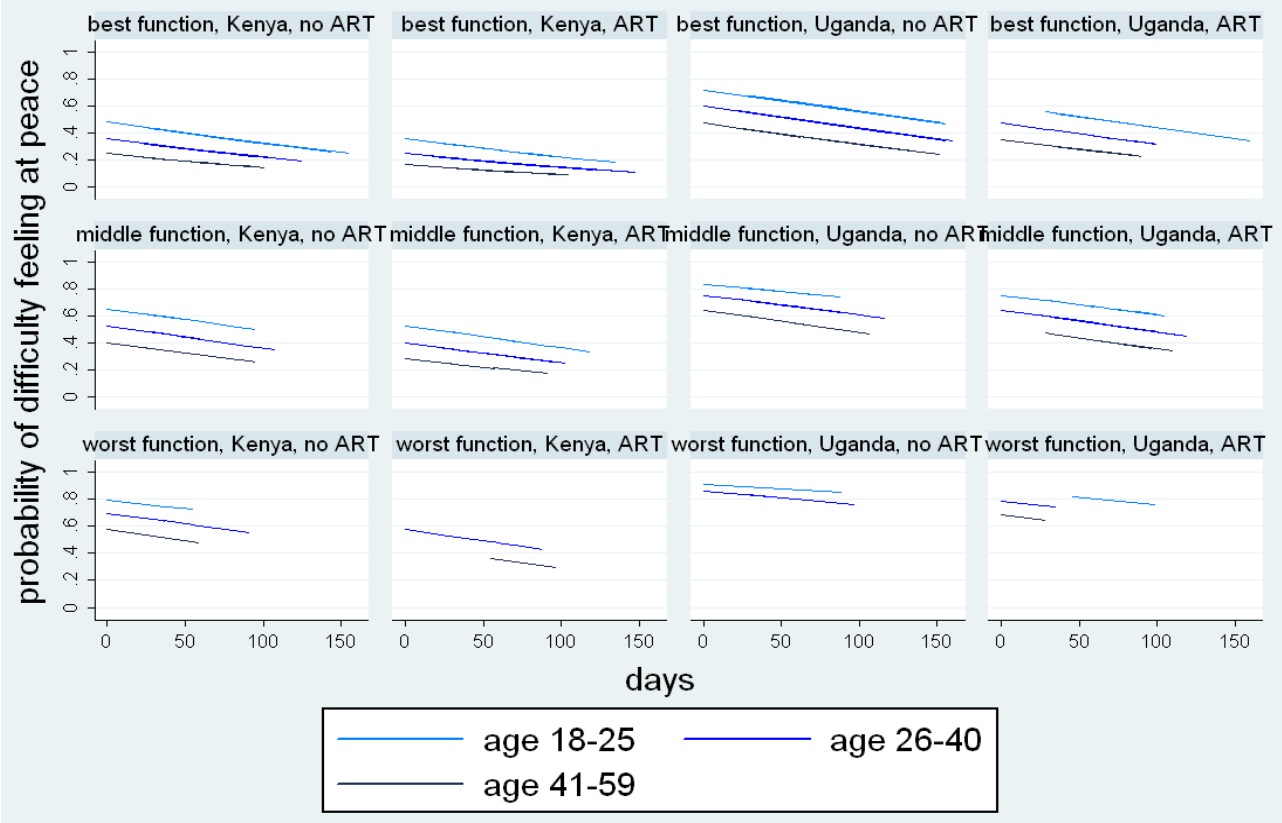
In bivariate analysis, age, physical function, county and ART use were associated with the probability of problems feeling at peace(Table F-55). Significance was very high for all four (p<0.001). These covariates were carried forward into multivariate analysis.

Table F-56: results of population-averaged multivariate logit model of prevalence of problem feeling at peace

	Log OR	SE	Z	p	OR	95% CI of OR
Days since T0	-0.007	0.001	-4.84	<0.001	0.99	0.99-1.00
Age	-0.515	0.124	-4.15	<0.001	0.60	0.47-0.76
Physical function	0.700	0.111	6.34	<0.001	2.01	1.62-2.50
Country	0.991	0.151	6.56	<0.001	2.69	2.00-3.62
ART use	-0.508	0.130	-3.91	<0.001	0.60	0.47-0.78

Table F-56 shows that all covariates are significantly associated with the odds of peace, suggesting little association between covariates. The prevalence of problems decreases over time. Each level of impairment in physical function doubles the odds of problems feeling at peace (OR=2.01) and country has an even bigger effect (OR=2.69). Younger people and those not taking ART have higher odds of problems.

Figure F-19: predicted response curves for the model in Table F-56



Four covariates were associated with the probability of problems feeling at peace over time, with country having the largest effect. All distributions overlapped with each other, and so the model could only be represented by using twelve graphs(Figure F-19). They show that people who with the worst physical function who lived in Uganda, and did not take ART were almost certain to have problems feeling at peace at recruitment. The slope was steeper than that for sharing feelings but relatively flat compared to other items, showing that problems feeling at peace did not change a great deal over time.

F.8.vii Difficulty obtaining help and advice

In bivariate analysis, country was strongly associated with the prevalence of problems obtaining help and advice (OR=3.36, p<0.001). ART use had an equally high significance but a weaker OR (OR=0.63, p<0.001). Education and wealth quintile were also associated with the outcome.

Table F-57: results of population-averaged logit models fitting one variable at a time to prevalence of problem getting help/advice, with 0/1 as baseline

	Log OR	SE	Z	p	OR	95% CI of OR	Carried forward
Gender	-0.070	0.170	-0.41	0.683	0.93	0.67-1.30	No
Age	-0.092	0.135	-0.68	0.496	0.91	0.70-1.19	No
Wealth quintile	-0.081	0.058	-1.38	0.166	0.92	0.82-1.03	Yes
Education	-0.311	0.109	-2.85	0.004	0.73	0.59-0.91	Yes
Physical function	0.068	0.122	0.55	0.580	1.07	0.84-1.36	No
Country	1.211	0.177	6.83	<0.001	3.36	2.37-4.75	Yes
ART use	-0.466	0.131	-3.55	<0.001	0.63	0.48-0.81	Yes

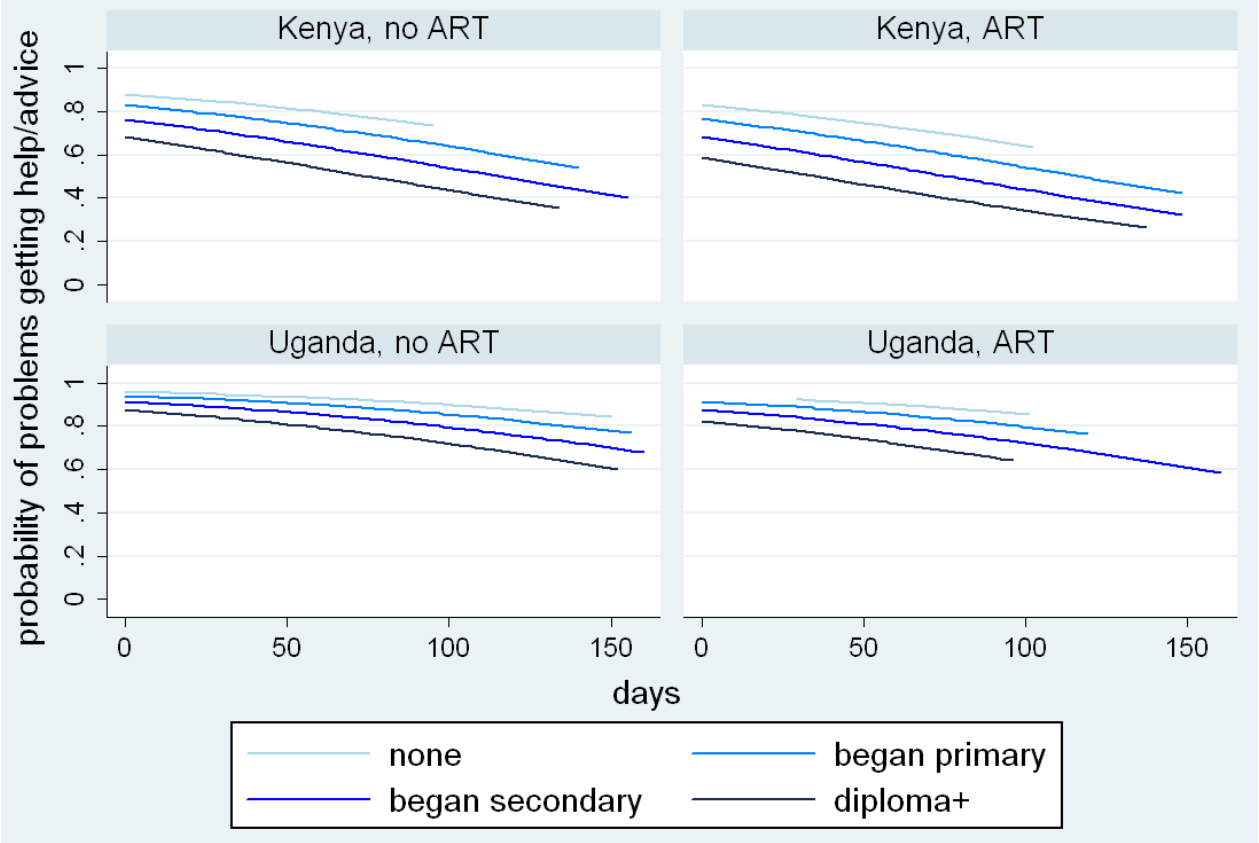
The four variables wealth quintile, education, country and ART use were fitted in a multivariate model. Wealth quintile was then removed, because it was not significantly associated with outcome (OR=0.94, p=0.283). The final model is shown in Table F-58.

Table F-58: results of population-averaged multivariate logit model of prevalence of problem getting help/advice

	Log OR	SE	Z	p	OR	95% CI of OR
Days since T0	-0.010	0.002	-6.28	<0.001	0.99	0.99-0.99
Education	-0.415	0.108	-3.84	<0.001	0.66	0.53-0.82
Country	1.193	0.178	6.70	<0.001	3.30	2.33-4.68
ART use	-0.404	0.138	-2.93	0.003	0.67	0.51-0.87

Education and ART use have a small but significant effect on the odds of problems obtaining help/advice, while country has a much larger effect (OR=3.30).

Figure F-20: predicted response curves for the model in Table F-58



The predicted probabilities from Table F-58 are displayed in Figure F-20. Problems became less prevalent over time. In Kenya change is quite linear but in Uganda it increases over time. Participants on ART had fewer problems accessing help and advice. Problem start from a very high prevalence, particularly in Uganda where the probability is almost 100% at baseline for those not taking ART.

F.8.viii Summary of risk factors over time and compared to baseline

Table F-59 below summarises the findings of multivariate longitudinal analysis. Taken as an average, all outcomes improve over time at the individual level. The effect of time has high significance but a very weak OR. The difference between outcomes in terms of change over time cannot be observed within two decimal places.

The independent variables of most importance in predicting outcomes are physical function, country, wealth quintile and ART use. These variables are associated with multiple outcomes across different domains of care. By contrast, gender and education are each associated with only one outcome, and age is associated with two which are similar to each other (difficulty finding life worthwhile and finding peace).

Limited physical function is associated with more problems in five areas, and fewer problems sharing feelings, and is not associated at all with access to help/advice. Physical function is more strongly associated with symptoms and pain, the physical problems, than with other outcomes. Ugandans have more problems than Kenyans in five outcomes, especially in psychological and spiritual domains, where the effect is strong. ART is associated with fewer problems in three areas: symptoms, finding peace and obtaining help and advice. These three represent respectively physical, spiritual and social problems and their score distributions in previous analysis are very different from each other. The OR is fairly similar for all three, ranging from 0.60 to 0.68.

Men and women have similar problems except that there is a weak effect for women to have more worry, while older age is associated with less spiritual and existential burden. More educated people are better able to obtain help and advice. Increased wealth is weakly associated with reduced odds of pain, symptoms and difficulty finding life worthwhile, but increased difficulty sharing feelings. Ability to share feelings is an exception to several trends, being more of a problem for wealthier people with the best physical function.

In cross-sectional analysis the results for pain and symptoms were very similar to each other, but here, although they still have similar odds ratios for the relationships with wealth quintile and function, symptoms are also more common in Uganda and less common with ART, while pain is not associated with either. The only two outcomes to share the same combination of covariates are pain and ability to share feelings, and they are opposed to each other. Poverty and limited function make pain worse but make it easier to share feelings. The only common trends are in the

covariates, rather than the outcomes. In general terms, poverty, younger age, limited physical function, residence in Uganda and lack of ART are risk factors for multidimensional problems.

The results from the two summary tables of longitudinal analysis, Table F-35 for Part B and Table F-59 for Part D, are combined in Table F-60. In many respects they are similar. Variables associated with an outcome cross-sectionally are likely to also be associated with change in the outcome over time.

The two countries have symptom and worry scores that are similar at baseline, but over time people in Uganda have a greater probability of physical symptoms and worry. At recruitment, women have more difficulty sharing their feelings, with a strong OR, but this effect disappears over time. Wealth quintile is associated with difficulty sharing feelings over time, but the effect is very weak, given that an ordinal, evenly distributed variable such as wealth quintile is very effective at detecting an association. Problems finding life worthwhile are not associated with physical function at diagnosis but over time, those with limited function have more problems. Conversely, those with limited physical function report fewer problems obtaining help and advice at baseline, but this effect is lost over time.

Table F-59: summary of multivariate associations between independent and dependent variables over time

Reference group	***Gender*** **Male**	***Age*** **18-25**	***Education*** **None**	***Wealth quintile*** **Lowest**	***Physical function*** **Best**	***Country*** **Kenya**	***ART*** **No**	***Time***
Pain				0.81*** (0.73-0.89)	2.83*** (2.27-3.52)			0.99***
Symptoms				0.89* (0.80-0.99)	3.09*** (2.47-3.88)	1.36* (1.00-1.84)	0.68* (0.51-0.92)	0.99***
Worry	1.34* (1.01-1.79)				1.57*** (1.28-1.94)	1.60** (1.21-2.10)		0.99***
Sharing feelings				1.15** (1.04-1.27)	0.69** (0.56-0.86)			1.00**
Life worthwhile		0.67** (0.52-0.86)		0.78*** (0.70-0.87)	1.63*** (1.31-2.02)	2.83*** (2.09-3.84)		0.99***
Peace		0.60*** (0.47-0.76)			2.01*** (1.62-2.50)	2.69*** (2.00-3.62)	0.60*** (0.47-0.78)	0.99***
Help and advice			0.66*** (0.53-0.82)			3.30*** (2.33-4.68)	0.67** (0.51-0.87)	0.99***

‘*’= p<0.05 ‘**’=p<0.01 ‘***’=p<0.001

Table F-60: summary of cross-sectional and longitudinal associations with independent variables

Reference group	*x-sect or long*	*Gender* **Male**	*Age* **18-25**	*Education* **None**	*Wealth quintile* **Lowest**	*Physical function* **Best**	*Country* **Kenya**	*ART* **No**
Pain	X				0.79(0.69-0.91)	3.19(2.30-4.43)		
	L				0.81(0.73-0.89)	2.83(2.27-3.52)		
Symptoms	X				0.86(0.75-1.00)	3.15(2.26-4.41)		
	L				0.89(0.80-0.99)	3.09(2.47-3.88)	1.36(1.00-1.84)	0.68(0.51-0.92)
Worry	X	1.62(1.10-2.37)				1.56(1.16-2.11)		
	L	1.34(1.01-1.79)				1.57(1.28-1.94)	1.60(1.21-2.10)	
Sharing	X	1.75(1.21-2.53)				0.51(0.38-0.69)		
feelings	L				1.15(1.04-1.27)	0.69(0.56-0.86)		
Life	X		0.66(0.47-0.92)		0.78(0.68-0.90)		2.10(1.41-3.12)	
worthwhile	L		0.67(0.52-0.86)		0.78(0.70-0.87)	1.63(1.31-2.02)	2.83(2.09-3.84)	
Peace	X		0.30(0.16-0.58)[a]			1.70(1.27-2.28)	2.31(1.60-3.34)	
	L		0.60(0.47-0.76)			2.01(1.62-2.50)	2.69(2.00-3.62)	0.60(0.47-0.78)
Help and	X			0.54(0.41-0.70)		0.62(0.45-0.84)	2.65(1.75-4.02)	
advice	L			0.66(0.53-0.82)			3.30(2.33-4.68)	0.67(0.51-0.87)

[a] age 41-59 compared to age 18-25

G Discussion

In this chapter, the findings from all four parts of the analysis (A – univariate at baseline, B – multivariate at baseline, C – univariate over time, and D – multivariate over time) are first summarised in order, then grouped by outcome and appraised. The strengths and limitations of the study are assessed and in light of these, the implications for practice, policy and research are drawn out.

G.1 Summary of main findings by objective

The main findings are presented by objective below.

Objective 1: To determine prevalence and severity of palliative care-related problems within two weeks of diagnosis of adults with HIV in Kenya and Uganda

The findings show a large burden of palliative care-related problems at HIV diagnosis, in all areas, but especially in the social domain. Bearing in mind that the study sample consists of relatively young adults with good physical function recruited from the general population and in the so-called asymptomatic stage of a manageable condition, the burden of palliative care-related problems is severe.

- *Objective 2: To investigate whether demographic variables or CD4 count are associated with prevalence and severity of palliative care-related problems at diagnosis*

The cross-sectional analysis of key independent variables shows some over-arching trends. Patients with impaired physical function have more physical, psychological and spiritual problems, but fewer difficulties getting help and advice or sharing their feelings. Those of lower socioeconomic status are more likely to

have physical and existential problems. Psychosocial and spiritual problems are more severe in Uganda than Kenya, and older people seem to be less troubled by spiritual problems.

Objective 3: To determine change in palliative care-related problem severity over a three month period

During three months under care, all problems are reduced for the sample as a whole. Physical problems (pain and symptoms) improve most rapidly, with the majority of gain within the first month. The more existential and interpersonal problems (being able to share feelings, feeling life worthwhile and being at peace) show less change over time and improvement occurs more slowly. Problems sharing feelings are resolved more in the second month than the first. In the third month, problems feeling at peace increase again.

Objective 4: To investigate whether demographic variables or ART use are associated with change in palliative care-related problem prevalence over time

Patients with physical impairment experience less reduction in most problems, but have less difficulty sharing feelings over time. Those of higher socioeconomic status report greater pain reduction over time and fewer problems finding life worthwhile but have more difficulty sharing feelings. Being on ART is associated with gains in several areas but the effect has weak significance. Psychological and spiritual problems are maintained for longer in Ugandan patients. Women report more worry over time, while more educated people have fewer problems obtaining help and advice. Older people have fewer spiritual and existential problems over time.

G.2 Recruitment, retention and representativeness of sample

Full retention, defined as completion of four interviews, was 75% (n=325). This is a relatively high retention rate(337), improving the generalisability of results. However, the 25% who completed fewer observations are likely to be different from those who completed all four in ways that may bias the results. LTFU was normally recorded as ‘reason unknown’. This suggests that the participant was not seen by the HCW who collected the data, as the HCW would have attempted to learn and code a reason. It follows that the lost participants probably did not come to the health centre at all. Thus, the majority of patients lost to study follow-up probably experienced a hiatus in their care. This is speculation based on an absence of data, but high attrition from HIV care is common, especially for patients not receiving ART(321).

The reasons for programme attrition have been examined in terms of structural barriers(342), psychological factors(147), and pragmatic behaviour change(343). A major structural barrier is the cost of transport to the care facility(154). In the study, patients were reimbursed the cost of transport, but this does not entirely remove the barrier. It was still necessary for patients to pay for transport to the health facility up front and some may not have been able to do so. In the qualitative interviews in Phase 1 of the PEPFAR PHE, patients reported that expenditure in terms of time is another problem, as clinic visits (plus transport and waiting times) frequently take all day, meaning the loss of a day’s work. Symptoms may also hinder retention. Fatigue is one of the most common symptoms of HIV(58); patients may lack the energy to undertake the journey. One of the precoded options for the reason for LTFU was ‘unable to return to health centre’. This was rarely reported, but that could be because in the event that patients could not return, information to that effect would not have reached the health centre.

An unknown proportion of those lost to follow-up were still receiving care but chose not to participate in the study. In Africa, the proportion of potential recruits who consent to join a study is generally much higher than in Europe. Possible reasons for this include the perverse incentive of a cost reimbursement; the hope of improved care; and a cultural expectation of deference to the authority of health providers. The number of refusals was not recorded, but from discussion with the

research assistants it was clear that very few patients refused to participate. It is possible that participants left the study either because their hopes of better care or other incentives were not materialised, or because they had never wanted to participate and had consented out of obedience. Therefore, drop-out could constitute a form of refusal by default.

Retention is not a study outcome because it was manipulated by the design. Participants were paid US$5 to reimburse the cost of travel at follow-up appointments, and therefore had an additional incentive to return to the health facility. However, there is evidence that multidimensional problems can be a cause of LTFU. In focus group discussions, patients in Tanzania reported that pain, sickness, hunger and loss of hope were obstacles to retention(147). A meta-ethnography of qualitative studies of HIV care attrition found that one reason patients do not return to the health centre is lack of perceived benefit(151). Palliative care delivers patient-centred improvements, which could encourage patients to remain in care, with consequences including improved health and reduced mortality(141).

G.3 Multidimensional problems at and following HIV diagnosis

The findings relating to each of the seven outcomes are considered one by one, followed by a discussion of the total POS score, and of similarities and differences between outcomes.

G.3.i Pain

As in other diseases, HIV pain has many possible causes and presentations. A study of AIDS patients in Denmark(344) found 69% of patients had constant pain interfering with daily living. The most common type was neuropathic pain in the extremities, but other causes included opportunistic infections, lymphoma and Kaposi's sarcoma. In South Africa, the most common sites of pain for AIDS patients were the lower limbs(66%), mouth(51%), head(43%) and throat(40%)(45). Common causes of mouth and throat pain are oral candidiasis, herpes simplex and Kaposi's sarcoma. Headaches could be due to infection, tumour, sinusitis, systemic infection or stress. Chest pain is frequently caused by tuberculosis and respiratory infections(344).

Sensory neuropathy is a common and painful problem, affecting around 40% of people taking ART(345). The first line therapies recommended by NICE for painful HIV sensory neuropathy are pregabalin and amitriptilyine, but a recent systematic review found that neither performed any better than placebo(345). The only therapies to show an effect were cannabis, Nerve Growth Factor and topical capsaicin, and the effect of opioids had not been studied.

At baseline, 66.9% of participants reported pain, and 19.4% a pain score of 3, 4 or 5, denoting more severe pain (up to overwhelming pain at 5). These figures are comparable with the findings from outpatients in India of 53% pain (302) and 31% severe pain(301), shown in the systematic review chapter. The only information on pain prevalence among newly diagnosed outpatients in a low-income country is a report of 76% prevalence for AIDS patients in Uganda(298). In this thesis, of a group of outpatients with good physical function and access to care, over two thirds

report pain in the first two weeks after HIV diagnosis, which is not much lower than the prevalence among people with AIDS. Indeed, the definition of AIDS in the paper was a CD4 below 200, which was a criterion for ART initiation in the eleven health facilities where data were collected. Since neither CD4 count nor ART was associated with pain, the results suggest that pain is relatively common in all disease stages, and highly prevalent at diagnosis.

Participants from higher socioeconomic quintiles were less likely to report pain, both at baseline and over time, possibly because they were able to pay for pain relief. In both Kenya and Uganda, essential drugs should be freely available through health centre pharmacies. However, supply does not meet demand, and stock-outs are a frequent problem(346). A pharmacy review prior to the longitudinal study showed that in Uganda, all five health facilities represented here had the weak opioid codeine in stock, but three had run out within the previous three months(347). Only two facilities stocked morphine and one of them had experienced a stock-out. In Kenya, four of the six facilities had codeine, one reported a stock-out, and none had morphine(346). These supply problems reflect national trends. In this situation, patients have no option but to take their prescription to a private pharmacy and pay for the drug.

Interestingly, socioeconomic quintile was only associated with the odds of moderate pain at baseline, and not with the odds of severe pain. A possible explanation for this is that opioids for the treatment of severe pain are not available privately, and so wealth is no advantage to obtaining them. Analgesics for moderate pain can be bought privately, and wealthier people may be able to seek health care at an earlier stage, so wealth would be of benefit. Moderate pain may also be more amenable to non-pharmacological therapies or more likely to be self-limiting.

Although poverty is a risk factor for pain and physical symptoms, cash transfer is unlikely to be an appropriate response. Cash transfer schemes are a medium to long term intervention, mainly aimed at prevention. It is impossible by definition to identify people beforehand who may be at greater risk of symptoms at diagnosis. If they could be so identified, they would be diagnosed at the time. Free care is easier to deliver and more likely to be effective than cash transfer.

Pain scores improve in the first and second months after diagnosis, but in the third month, net change is negative, showing that pain worsens a little. A floor effect could have contributed to this finding. As an increasing proportion of patients reached a pain score of 0, the possibility of further improvement disappeared, thus a small and non-significant increase in pain might be the result of regression to the mean. However, at the individual level, while the proportion of people whose scores improve falls from 39.5% in the first month to 24.9% in the third, the number whose pain gets worse rises from 19.7% to 26.9%. A floor effect would not predict this. Overall, 19.9% of the sample report more pain at M3 than at baseline.

A possible explanation is that the majority of pain was managed with non-opioids, but second-line treatments were not available (i.e. the WHO pain ladder(12) was not followed) for patients whose pain recurred. A small number of patients reported severe pain at diagnosis which was not relieved over time. A pharmacy review for Phase 1 of the PHE found that only two facilities stocked morphine(348), and these patients in severe pain may have needed morphine and been unable to access it. They could also have been suffering from neuropathic pain which is only partially responsive to opioids.

The use of opioids is extremely low in both study countries and in Africa as a whole, which consumes ten daily doses per million people per day, compared to 1564 per million per day in North America(349). Uganda and Kenya are respectively the fourth and sixth largest consumers of narcotics in sub-Saharan Africa (behind South Africa, Namibia, Botswana, and Zimbabwe at fifth) but they rank 132nd and 134th worldwide. As a consequence, effective pain relief is very difficult. A Human Rights Watch report highlighted the failure of health services in Kenya to provide pain relief for children(350).

Despite the low use of morphine, Uganda is in fact a model of opioid availability in Africa, as it was the first country to permit nurses to prescribe morphine(228). So far, only a small number of health services have made use of this option. Reasons for under-provision, identified in both Uganda(351) and Kenya(350), include:

- Physicians' reluctance to prescribe opioids, believing them to be dangerous or addictive

- An unclear legal situation with heavy penalties for of opioids
- Strict regulations to prevent smuggling and misuse, with can hamper legal prescription
- Lack of centralised supply in Kenya
- Difficulty meeting the requirements for storage, such as double-locked cabinets

Interventions have not been studied in this thesis. The assumption in the preceding paragraphs is that pain scores were reduced because pain was managed with medical intervention. There may also be a form of regression to the mean, if pain is one of the factors motivating people to go for an HIV test. In that case, the time of diagnosis would be associated with a higher than average level of pain. However, non-opioid analgesics are one of the most common therapies and pain is highly prevalent in HIV, so it seems likely that most of the reduction was caused by health care at the eleven facilities.

In the multivariate longitudinal analysis, pain over time is more likely for patients who are poorer and especially those with impaired physical function. There is a weak trend for older people to have a higher risk of pain, and ART is not associated with the outcome. A two-year study in Kenya also found that pain prevalence was not reduced by ART(352), although ART is expected to reduce the frequency of infections which could cause pain. A possible reason for the lack of association is that ART initiation can be accompanied by immune reconstitution inflammatory syndrome (IRIS), as the recovering immune system starts to respond to previously undetected pathogens(353). Neuropathy is also a side effect of ART(354).

Pain may be considered the most discrete and classifiable of the seven multidimensional problems examined in this thesis. However, what patients mean by ‘pain’ is not necessarily a physical problem, and pain has been defined as ‘what the patient says hurts’(355). Dame Cicely Saunders developed a model of ‘total pain’, showing that physical, psychological, spiritual and social problems could not necessarily be disentangled. The conclusion of the total pain theory is that physical pain cannot be adequately managed in isolation, without treatment of non-physical pain. Similarly, a review from South Africa said HIV pain treatment should be

“pharmacological, psychotherapeutic, cognitive-behavioral, anesthetic, neurosurgical, and rehabilitative”(37). Ongoing or recurrent high pain scores may have reflected a non-physical pain which patients expressed in this way.

G.3.ii Symptoms

In this sample 65.8% of participants were affected by symptoms at baseline, 14.4% reporting a score of 3, 4 or 5. The results for symptoms are similar to those for pain, unsurprisingly, as the two often co-occur and pain can be considered simply a particularly common and burdensome symptom. As with pain, a small proportion of people appear to have intractable problems while most improve over time. The results of Part C show that the majority of symptoms are managed quickly, within one month. After the first month, symptom burden continues to reduce but at a much slower pace, and a small minority continue to have high, unalleviated symptom burden.

One third of participants do not report symptoms at baseline, and similarly one third do not report pain. However, the POS covers only a three-day interval, being designed to detect short-term change. HIV is characterised by an illness trajectory which is not steep and sudden as in cancer but unpredictable and fluctuating. It is very likely that if the time period for symptom detection had been extended further a higher prevalence would have been found.

The PHE did not gather any information on the types of symptoms experienced. In the systematic review, common symptoms include fatigue, fever, itching, weight loss, diarrhoea, cough and skin problems. The most similar population to report symptoms found in the systematic review is a group of people with AIDS in Uganda, in which the prevalence of symptoms was 67% itching, 61% tiredness, 53% cough, 52% skin problems(298), 35% STI symptoms(299).

Symptoms can be caused either by HIV itself, by opportunistic infections or by comorbidities. Conditions which appear to be independent comorbidities have been found to be linked to HIV. For example, people with HIV are at greater risk of

malaria(356), thus a malaria symptom such as fever is a part of HIV management because HIV increased the person's risk of developing the symptom. Given that the number of conditions for which HIV is known to increase susceptibility is constantly expanding, it is practically impossible to separate HIV symptoms from non-HIV symptoms, and a patient-centred approach does not require the distinction to be made. All symptoms reported by HIV patients are relevant to HIV palliative care. HIV symptoms appear to be more frequent and to appear earlier in the disease trajectory in Africa than in high-income countries(357, 358). This was originally thought to be evidence of a more virulent strain of HIV but is now thought to reflect the higher background prevalence of infections and general morbidity(359).

At baseline, pain and symptoms are both associated only with wealth quintile and physical function. Physical function has a strong effect (OR=3.2 for both), showing that people with limited physical function, and especially those with the worst, are at a much higher risk of pain and symptoms. It is likely that to some extent this direction should be reversed; people with a heavy symptom burden have reduced physical function. A simple screen of physical function by health care workers could be useful to identify the patients at highest risk of pain and symptoms.

Participants with limited physical function are likely to have a restricted ability to work, as shown in South Africa(360) and inferred in Kenya(352) from ART initiation studies. Decreased productivity puts patients at risk of poverty, debt and other social problems. A defining feature of extreme poverty is that a high proportion of income is spent on food(114), limited income due to ill health is a direct cause of malnutrition and further limits ability to work(112). Lowered work productivity due to HIV is recognised as a major stress on family income and arguably the primary threat to integrity of a family unit(115). Lack of food is also an established cause of non-adherence to ART, as patients do not take twice-daily medication if they only have enough food for one meal per day(361). The necessity of poverty alleviation as palliative care was graphically described in the case of Zimbabwe:

> *"Controlling pain and leaving the patient with severe hunger pangs seems pointless as does empowering the family caregiver with basic nursing skills when they do not have the energy to turn the patient because they too are starving."(362)*

The association of physical domain outcomes (pain and symptoms) with wealth quintile is relatively weak. Wealth quintile, as a variable, is optimally designed to detect any association. It consists of five categories of equal size, and therefore weight, analysed as a continuous ordinal variable. Any trend or deviation from pure randomness in the relationship between the outcome and wealth quintile would probably be detected, but none is. The fact that there are five categories limits the strength needed to show significance, but it also limits the strength likely to be found. Weak associations are detected and may not mean a great deal.

During these three months, all participants were receiving HIV care (not palliative care) and a high proportion of them were initiated on ART. It is not possible to determine the proportion of symptom reduction attributable to ART, to symptom-specific care, to treatment of causes (e.g. TB treatment against cough) or to a self-limiting effect over time.

The longitudinal results show that people taking ART have fewer symptoms over time, but the effect is small, and much less than the effect of physical function. There is evidence from Kenya that ART is associated with reduced symptoms(352), with two caveats; pain and fatigue remained common throughout the two years of observation, and improvement was at the level of the individual. Similarly, in this study, pain was not associated with ART use although other symptoms were. People taking ART generally have more advanced disease than those not taking ART, and therefore, even though symptoms decrease for them over time, they may still have more symptoms and worse physical health than other patients with HIV(363). In South Africa, a cross-sectional study found that people taking ART had fewer physical symptoms and were better able to work.

Physical symptoms and pain are often overlooked in the earlier stages of HIV, which are inaccurately described as ‘asymptomatic’(364). Assessment and management of symptoms for HIV outpatients in Africa is also lacking. These results show that pain and symptoms are prevalent and severe, and require assessment and treatment as soon as practicable after HIV diagnosis and regularly over time. However, compared to the other dimensions of care (psychological

spiritual and social), the physical dimension is the place of fewest problems. All other multidimensional problems are more severe, both at baseline and over time.

G.3.iiiWorry

In this dataset, worries are more prevalent and severe than physical problems at HIV diagnosis. Over two thirds of participants are worried at diagnosis, 11% of them scoring 3, 4 or 5. Participants with limited physical function and women are more likely to worry. These two associations have an equal strength and similar significance. Unlike the physical domain outcomes, there is no evidence that poorer people are more likely to worry.

In the literature, the systematic review results of worry at diagnosis show that in Uganda, 51% of outpatients with AIDS were worried(298). The population with AIDS may be similar to those with limited physical function in the current study. In Rwanda, 80% of pregnant women said that their HIV diagnosis caused them a great deal of concern(65).

Overall, worry is reduced over time, with the great majority of improvement occurring in the first month. A small group of people continue to have severe worry up to M3. Between M2 and M3, 58.2% of participants experience no change in worry score, which is the highest proportion to show no change of all seven outcomes except for feeling life worthwhile (60.7%). These findings suggest that while many patients' initial worries at diagnosis reduce with time, some participants experience chronic, unrelieved worry.

Worry is one of two outcomes associated with gender cross-sectionally, and the only one to maintain the association over time. In the study, women are more likely than men to report worry. The descriptive results in Table F-19 help to illuminate the odds ratios for gender. The table shows that 40% of women report moderate worry compared to 28% of men, but women and men have a similar probability of severe worry (11.1% vs 10.1%). Meanwhile, 16% of those with middle physical function and 24% of those with the worst report severe worry. It is generally found

that women are more likely than men to report worry, although whether they experience more worry or are simply more willing to report it is very difficult to establish. It appears that women on average worry more than men in this sample, but the highest levels of worry are uncommon in both genders and are more often associated with additional burdens, such as limited physical function. The direction of this relationship cannot be ascertained from cross-sectional data. To some extent, worry may impede functioning, but it is also likely that people with limited function have more problems (they are known to have more physical symptoms) and fewer resources, and so worry more.

The reduction in worry over time is associated with gender and physical function (also seen in the cross-sectional association at baseline), and also country, with Ugandans more worried than Kenyans. The fact that worry is associated with country longitudinally but not at baseline suggests that the difference between the two countries increases over time, as Kenyans improve more rapidly than Ugandans. The difference could be due to cultural or community response to HIV or care may be better at the six Kenya health facilities than the five in Uganda. A Client Services Receipt Inventory was used in the PEPFAR evaluation to record care received, but the version had several limitations. Scoring is binary (care components are either received or not received in a given month) with no indication of dosage, effectiveness or need. It was designed in this way for a wide-scale survey of 120 sites so that data could be combined and analysed, but the detail of care provision was lost in the process. As a consequence, the results are difficult to relate to outcomes.

Worry is a normal appropriate human response to news such as an HIV diagnosis and the existence of worry in the sample is entirely expected. Those with exacerbated worries may have them because their circumstances are more difficult or possibly because of a mental health problem. The POS is not diagnostic of anxiety disorder or of any other psychological condition. The APCA African POS has not been tested in a reference healthy population, so ‘normal’ worry scores are unknown. In any case the distinction between ordinary worry and pathological worry is unclear, which is frequently a problem in both research and clinical care(365). The 2001 WHO Global Health Report on mental health represents depressive symptoms as a continuum from ordinary mood fluctuations through

sustained mood change to a point at which symptoms interfere with life activities(366).

People with HIV are at heightened risk for anxiety, which may also predate HIV diagnosis(365). A nationally representative survey of people with HIV in the USA found 16% prevalence of anxiety (eight times higher than general population)(367). Using these figures, it is not possible to distinguish psychiatric morbidity as a risk factor for HIV infection from HIV as a risk factor for psychiatric problems. In Africa, the former is likely to be less pronounced, because the much higher population prevalence of HIV will reduce the excess risk caused by any single risk factor. In South Africa, 7% of 149 people within a year of HIV diagnosis had anxiety disorder(71). In India, 36% of outpatients had anxiety disorder at diagnosis(301). Biological effects of HIV also contribute to anxiety and depression, as HIV invasion of the central nervous system causes neurotoxicity in sub-cortical areas of the brain(82).

Anxiety disorders and depression are more common in women than men, both generally(366) and with HIV(368). Brandt argues that women, particularly HIV positive women, are more affected by poverty than men (369). In my results, disability (limited physical function) is an independent risk factor for severe worry and being female is a risk factor for moderate worry, which may not have been detected in studies that used less sensitive instruments or a smaller sample. Anxiety and fear were shown to decline over time in a series of studies in the early 1990s(263, 305, 306, 370).

G.3.ivDifficulty sharing feelings

A patient who has difficulty sharing their feelings with the people around them has limited access to emotional support. Emotional support for people with HIV is strongly associated with physical and psychosocial adjustment. In Europe, people with HIV who are satisfied that they have enough emotional support report enhanced quality of life and self-esteem(371). One of the main reasons that people

with HIV disclose their status to others is so that they can receive emotional support(372).

The analysis for the outcome of difficulty sharing feelings revealed three unusual characteristics. Firstly, problems are highly prevalent and very severe. Almost 90% of participants have difficulty sharing their feelings at baseline, and 32% report not being able to tell anyone how they were feeling in the previous three days. Such a high level of problems is only exceeded by one other outcome (help and advice).

Secondly, the largest proportion of change over time occurs in the second month after diagnosis, not the first month as with the other six outcomes. Over a third of people (36.1%) report that sharing feelings becomes easier during the first month, but almost as many say it is more difficult, leaving a net improvement of only 3.7%. Proportion of net change is significantly better (i.e. the confidence intervals do not overlap) in the next two months, with 11.6 and 7.5 net change respectively.

Thirdly, the covariates which usually predict greater problems are associated with this outcome in the opposite direction. At baseline, better physical function is associated with more problems sharing feelings. Over time, people with the best physical function and the highest relative wealth have the most problems.

Difficulty sharing feelings has the lowest proportion of net change of all seven outcomes. The reason is that while a fairly typical 41% of people report better scores over time, 30% report that their problems get worse. Unlike the distribution for worry, where most scores changed very little, scores for this outcome fluctuate between extremes throughout the study period. Table F-40 to Table F-43 show that of the seven outcomes, it is the one in which scores are most likely to increase or decrease by four or five points in a month, moving the full range of the scale. Supporting this result of low net change, the longitudinal analysis in Part D produced graphs with a very shallow curve, showing little change over time. Difficulty sharing feelings is the outcome with the second highest level of problems at baseline and therefore it has great potential for improvement over time, but this improvement does not occur. Progress is slow, many people find their problems are exacerbated over time, and ART has no effect.

These results suggest that being able to share feelings is a situation in flux. The item may have detected changing emotional state, rather than the more constant psychological trait detected by the worry item. Ability to share feelings about being diagnosed HIV positive may be a process, rather than an event, and it may change frequently, with unpredictable results over time. The prevalence, severity and persistence of problems show that this is a very important area for patients. Inability to share feelings causes emotional distress, who consequences include loneliness, isolation, lack of self-care, depression, and inability to access help(373). People with these problems are less likely to adhere to treatment or maintain contact with health services (374), and are at risk of accelerated disease progression(375).

Sharing feelings is more difficult for women than men at diagnosis(OR=1.75), but over time this association disappears. To share feelings openly implies disclosing HIV status. Consequences of disclosure can include ostracism, violence, and family rejection, particularly for women(122). Some studies have found that women are less likely than men to disclose their HIV status(368, 376), which would limit their ability to share feelings. A large study in Uganda found that 83% of both men and women reported disclosing to at least one person on the day they were diagnosed(377). These participants may not have been typical, as they received care through The AIDS Support Organisation (TASO), a grass-roots HIV service which places great emphasis on disclosure and family care. The study also did not indicate to whom participants had disclosed. Of 397 people with HIV in Kenya (72% female), 93% had disclosed their status to someone but only 27% had disclosed to their primary sexual partner(378), demonstrating that a high level of disclosure may coexist with the maintenance of secrecy. The present study did not record disclosure and so it is not possible to do more than speculate about the connection between ability to share feelings and ability to communicate HIV status.

Incidence of disclosure may be related to reason for testing. Voluntary testers may be more prepared to disclose their status, while women who test during antenatal screening are less likely to disclose their status than any other group(376). This could be because voluntary testers have previously considered what they would do if the test was positive and are more prepared for the diagnosis, whereas women

tested antenatally may lack the resources to disclose that information. Pregnant women may also have more reason to be afraid of family rejection.

The association between ability to share feelings and wealth quintile may be spurious. At baseline, those in the middle and fourth quintiles are more likely to have no/mild problem sharing feelings, compared to the two quintiles below them and the one above. The difference is significant in a chi squared test (p=0.041) but not in a test for trend (p=0.588), indicating a non-linear relationship, but given that wealth quintiles are created from a continuous variable formed in a principal components analysis, non-linear associations are unlikely. In the longitudinal analysis, ordered categorical variables are treated as numerical scales, without expansion terms to separate the categories. This means that the association with two quintiles appeared to be a trend across all five. It is also important to note that the coefficients for associations with physical function and wealth quintile are both relatively small. Perhaps the best way to interpret the findings is that anyone can have difficulty sharing their feelings, regardless of their circumstances or their previous scores.

An alternative explanation is that sharing feelings is easier when the problem is seen as ‘legitimate’, just as ‘invisible’ symptoms such as pain and fatigue are under-reported(379). The finding could also be due to a kind of response shift, in which other problems (such as pain, worry, or need for help and advice) take precedence over the need to share feelings. In the USA in 1995, men described as ‘symptomatic’ were more likely to have disclosed their status two to four months after diagnosis than those who were ‘asymptomatic’(290). These terms are not defined in the paper and are more likely to refer to WHO staging criteria than actual symptom experience. The study supports the finding that people with worse physical function have fewer problems sharing their feelings.

One problem with the question is that it is not clear whether sharing feelings openly with people other than family/friends, for example a counsellor, would be included. In palliative care, relationships between the patient and informal caregivers are very important. Sharing feelings with a member of staff, even a trained counsellor, would not be considered an adequate substitute for doing the same with people emotionally close to the patient. No further information was gathered on this

question, nor were demographic details such as marital status and living arrangements which might be used as an indicator of family closeness.

The effect of interventions is also unknown. Counselling would have been available and recommended for all study participants. The extent, quality, frequency and effectiveness of counselling or other care is unknown. It is not possible to determine to what extent the change in ability to share feelings was affected by the passage of time, by health care interventions, or by external circumstances.

G.3.v Difficulty finding life worthwhile

Psychological morbidity has been a neglected area of research in low- and middle-income countries(380), especially Africa(378). Reasons given in the literature include limited health services, lack of valid and appropriate tools(60), a cultural marginalisation of psychosocial distress symptoms, and, in Africa, a prioritisation of HIV-related medical treatment above psychosocial support programmes(368). This deficiency is reflected in the systematic review of multidimensional problems at HIV diagnosis, where the area of ‘wellbeing’, which was mapped on to ‘difficulty finding life worthwhile’, was the only dimension to have no relevant data from outpatients in low-income countries. The cross-sectional findings show it is a significant problem, as 21% of participants report a score of 3, 4 or 5 at diagnosis.

A recent study of people with HIV or cancer in South Africa and Uganda showed this area was significant to patients, who rated having a sense of meaning in their lives as more important than physical comfort or activity(88). Mean MVQoLI wellbeing score for the HIV patients was -1.75, the worst score of the five domains, and significantly lower than the score for the cancer group. In the sample as a whole (81% with HIV), 30% agreed or strongly agreed with the statement ‘I have less of a sense of meaning in my life now than I have had in the past’.

Difficulty finding life worthwhile can be considered psychologically as depressed mood or from a sociological perspective as a consequence of the threat to sense of self caused by HIV diagnosis. These two perspectives are discussed in turn.

1. Psychological perspective

This study found that emotional difficulties are frequent at diagnosis. Similarly, in the literature 47% of newly diagnosed people with AIDS in Tanzania felt sad(298) and in India 68% were unhappy most of the time(302).

Patient-reported outcome research is always vulnerable to issues of meaning and translation, and it is for this reason that validity and reliability of questionnaires must be demonstrated, preferably in the language and cultural context where the tools are implemented. In the area of emotional problems, these issues are particularly complex. Even if all the relevant information was provided in the papers it would be difficult to judge whether the Hindi word translated as unhappiness corresponds exactly with the Swahili word translated as sadness.

The results presented here are the first to demonstrate individual-level change over time in psychological outcomes and to measure them so soon after diagnosis. The time is clinically relevant because diagnosis is the point of entry to care and individual-level change is important because it reveals highly fluctuant patterns over time, and shows that life worth must be assessed not just once but repeatedly in order to identify problems.

At baseline, women are more likely to worry and to have difficulty sharing their feelings, but not to have difficulty finding life worthwhile. The lack of association is unlikely to be a result of underpowering, because gender is the only covariate to show no association with the life worth outcome in both cross-sectional and longitudinal bivariate analysis. One possible explanation is an unusually high level of problems reported by men, who may be particularly susceptible to suppressed sense of worth in life following an HIV diagnosis. The theory conforms with the consistent finding that men are less likely than women to test for HIV (even after adjusting for prenatal testing), and then to enrol in care or to initiate ART(15). Loss of life worth may prevent men from returning for care.

Cross-sectionally, country, age and wealth quintile are associated with the outcome. The association with country has the highest OR (2.10) and the lowest p-

value (<0.001), which suggests that the understanding of whether life is worthwhile may be affected by cultural values that differ between the two countries. Longitudinally, country still has the strongest effect. By contrast, age and wealth quintile show associations with high statistical significance but a weak OR, with the 95% confidence intervals reaching 0.90 in both cases. There is good evidence that age and wealth quintile are associated with the outcome but they do not appear to have much effect on it.

Poverty could affect the outcome through channels that may not be immediately obvious, such as nutrition. There is cross-sectional evidence that micronutrients have a protective effect on depressive symptoms, and therefore deficiency caused by a poor diet can inhibit the ability to find life worthwhile. An RCT in Tanzania found that micronutrient supplements for pregnant HIV positive women reduced depression symptoms and improved quality of life(381). In this 62% female sample, with a mean age of 33, it is very likely that a high proportion of women were pregnant, especially since they were defined by recent diagnosis and one of the most common reasons for HIV diagnosis in East Africa is antenatal care(16). The association between wealth quintile and finding life worthwhile could have been partly caused by nutrient deficiency. On the other hand, the outcome was not associated with gender, so if this explanation is correct, nutrient deficiency would have to be comparable in men and women.

The total proportion of net change over time is low (14.6%). Only two other variables have a proportion of net change below 20% (difficulty sharing feelings and feeling at peace), and both these variables are highly fluctuant, with many people showing improvement over time and almost as many showing added burden, leading to a small net gain. By contrast, feeling life worthwhile shows a small gain simply because there is little net change in the first two months and none in the third. The majority of people (61%) experience no change in their status during the third month, and a further 20% change their score by only one point. Severe problems persist over time for some individuals, even though on average the burden decreases. This lack of change suggests that it is more difficult to affect a person's sense of life worth than to manage physical and psychological symptoms such as pain and worry. Many people continue to have great difficulty finding life worthwhile and do not improve.

Change over time is associated with age, physical function, wealth and country, making up more independent variables than were associated with any other outcome. The association with ART has a p-value of 0.054, which just misses statistical significance. A larger sample might have shown that being on ART was associated with finding life worthwhile.

Not feeling life is worthwhile may be a normal response without any indication of mental illness, but it is also a characteristic of depression. In the UK version of the POS, a high score in the 'life worth' question is followed by a recommendation for a depression screen. It is critically important not to mistake a difficulty finding life worthwhile for clinical depression, and this study does not contain any diagnostic validated tool for depression. The APCA African POS does not even carry the same recommendation as the UK version. However, depression is common in HIV(76) is associated with accelerated disease progression, and is also difficult to measure, as many of the physical symptoms of depression can themselves be caused by HIV(382). Depression symptoms are predictive of unprotected sex and risky behaviours, leading to the risk of further transmission and re-infection(50). Thus depression is a key concern in HIV and is briefly discussed here.

A systematic review found evidence that 20% of people with HIV had deliberately harmed themselves and 29% reported suicidal ideation during the previous week(383). Furthermore, 9.4% of deaths of people with HIV were attributable to suicide. Africa accounted for only three of the 66 studies in the systematic review, reflecting the general deficit of HIV mental health research in resource-poor countries.

The literature shows a high burden of psychiatric morbidity associated with HIV in Africa, particularly in the first year after diagnosis. In a group of 46 HIV patients in Kampala, Uganda, 83% had psychiatric disorders, including 54% major depression (384). The only longitudinal study of depression identified in Africa was conducted by Olley et al, who recruited 149 HIV patients within a year after diagnosis in South Africa and interviewed them using the Mini International Neuropsychiatric Interview(MINI). More than half(56%) were diagnosed with a psychiatric disorder, most frequently major depression(35%), dysthymic disorder(22%) or PTSD(15%),

with anxiety disorder less common(7%)(71). Six months later, 65 of the group (with a similar morbidity profile to the other 84) were re-assessed, showing that 48% had a psychiatric disorder (statistically unchanged from the baseline prevalence), and 26% had depression(385). Depression at six months was predicted only by disability score (OR=1.29). The authors suggested that the very high prevalence of problems was caused by stigmatisation and stress in South Africa. Paired analysis was not conducted so there is no indication of individual-level change over time. In effect, these were two cross-sectional studies within the same small population, not a true longitudinal study.

2. Sociological perspective

The question of life worth and existential wellbeing can also be viewed from a sociological perspective. In this approach, life worth is threatened by loss of self-image and identity following HIV diagnosis. Biographical disruption theory posits that people associate their sense of self with their physical body, such that a loss of confidence in the body because of illness or disability is conceived as an attack on personal identity and self-worth(386). In the theory, the three elements of personal biography are conception of self, conception of body and biographical time; a person's self-identity rests in who she knows herself to be, her physical body and her memory. Chronic illness is viewed as a biographical disruption that breaks the chain uniting these three elements (273).

The meaning of an illness cannot be separated from its context, as meaning depends on the consequences and significance of the illness to the individual(387). The significance of an illness is affected by the imagery around the disease, which may affect how individuals see themselves and believe themselves to be perceived(386). For example, a diagnosis of arthritis legitimates the symptoms, contains the possibility of cure, and can be perceived as a relief(387). In the case of stigmatising conditions such as cancer, the significance of the disease is heightened and the main response may be grief(388). The meaning of an illness depends very much on culture. A study of chronically ill people posited the existence of an 'American way of illness', in which sense of self was based on the values of independence and Protestant work ethic. The results of chronic illness

(social isolation, restricted life, becoming a burden and being discredited) challenged these values and contributed to a loss of self and consequent suffering(386).

Stigma appears to have some universal traits, transcending culture. Invisible contagion, sexual transgression, and unnatural death are three of the most common sources of stigma, and HIV touches every one of these(389). In many contexts, HIV bears the stigma of moral judgements, separating ‘innocent victims’ of HIV from those seen to have brought it on themselves(34). Thus, HIV is likely to carry a great deal of significance and to be particularly disruptive to the sense of self, inhibiting the sense that life is worthwhile.

In Cape Town, internalised stigma (measured using a validated instrument(390)) was common in a convenience sample of 1063 people with HIV(391). Over a third(35%) agreed with the statement “I sometimes feel worthless because I am HIV positive”. Men were especially prone to internalised stigma; 51% of men versus 38% of women agreed that “it is my own fault that I am HIV positive” while 47% of men compared to 37% said “I feel guilty that I am HIV positive”. After adjusting for gender, ethnicity (black versus other) and physical symptoms, internalised stigma was associated with depression on the CES-D. To some extent this may be inevitable, as the Cognitive and Affective Depression Scale of the CES-D includes items like “I thought my life had been a failure”, “I felt that people disliked me”, which share common ground with internalised stigma. In the same way, some of the problems reported in response to the item ‘Have you found that life was worthwhile’ may be indicative of depression and some may be indicative of internalised stigma or other conditions. From a patient-centred perspective, all of these are equally important and whether they are caused by HIV or completely unrelated to it, they are still palliative care-related problems at HIV diagnosis.

The concepts of biographical disruption and biographical work have been directly applied to people with HIV in a qualitative study(35). This paper had some limitations, including an unexamined certainty that people with HIV who had not progressed to AIDS and did not have haemophilia had no health problems. It also excluded the newly diagnosed.

G.3.viDifficulty finding peace

Spiritual wellbeing is understood to comprise two components, existential wellbeing (a sense that life has meaning, purpose and value) and religious wellbeing (comfort derived from connectedness to a higher power)(392). Feeling at peace is strongly correlated with emotional and spiritual wellbeing in patients with advanced disease(280). At baseline, 75.6% of participants did not always feel at peace and 19.2% never or not very often felt at peace, therefore spiritual distress can be interpreted as highly prevalent and frequently severe in this population.

Peace outcome scores improve over time, but, interestingly, problems worsen in the third month. Only one other variable (pain) shows a worse score in M3 than M2, and in that case the change is very small and follows two months of great improvement. By contrast, problems finding peace increase more in the third month than they decline in the second. These findings may reflect a delayed spiritual crisis. While other outcomes are most severe at diagnosis, difficulty feeling at peace recurs in the third month after HIV diagnosis, perhaps when the more immediate problems have been addressed. The study did not follow patients long enough to establish whether the spiritual problems in this second peak are managed. An HIV hospice study in the UK also found that while physical and psychological symptoms improved, spiritual problems were not resolved(393).

At baseline, peace is more likely for people who are older than 40, have best physical function, and live in Kenya. The same three variables plus ART use are associated with feeling at peace over time, but the graphs show the weaknesses of this model. The dataset was divided into 36 groups of very unequal size, two of which were empty (for example, no participants were Kenyan, aged 18-25, taking ART and reported worst physical function). In the smaller groups, particularly the findings for the worst physical function group, spurious results may have occurred. Nonetheless it is clear that age made a considerable difference (OR=0.6), with older people more likely to feel at peace. The descriptive analysis in Table F-29, and the results of the cross-sectional logistic regression, show that this effect is

probably driven by the oldest age group. People aged over forty are more likely to feel at peace than the other two age groups, despite having on average more limited physical function.

In qualitative interviews in South Africa, a patient with AIDS reported that physical, emotional, psychological and social problems inhibited spiritual wellbeing:

> *"No, I do not feel at peace because of the pain. I lack money for getting basic needs of life. The difficulty I have in feeding myself and the children makes me unhappy and therefore no peace."* (L. Selman, unpublished data)

The quote illustrates how different dimensions can interact to create the phenomenon of total pain.

Spiritual wellbeing is considered a state or outcome that can be achieved, whereas spirituality in general can incorporate beliefs, practices and a worldview(392), one aspect of which is religious belief and practice(394). The great majority of people in Kenya and Uganda, 87% and 86% respectively, say that religion is very important in their lives(395). In both countries, the majority of people define themselves as Christian, but often maintain a syncretic relationship with traditional beliefs, even when they might be considered incompatible. For example, 32% of Christians in Kenya and 53% in Uganda believe in reincarnation(395). HIV is sometimes thought of as a punishment for sin. When asked their opinion of the statement 'AIDS is God's punishment for immoral sexual behaviour', the majority agreed with it (71% in Kenya and 66% in Uganda), as shown in Table G-1(395). Thus a person newly diagnosed with HIV might feel guilt and shame over being punished, which would hinder peace.

Table G-1: 'Do you agree with the statement "AIDS is God's punishment for immoral sexual behaviour"?' Reproduced from Pew Forum 'Tolerance and Tension: Islam and Christianity in Sub-Saharan Africa'(395)

%	Completely agree	Mostly agree	Mostly disagree	Completely disagree	Don't know/ refused	n
Kenya	49	22	9	17	3	1500
Uganda	47	19	14	17	4	1040

In another example of syncretism, many people combine use of Western medicine with traditional healing, the most accessible and preferred source of health care in sub-Saharan Africa(396). A cross-sectional study of AIDS patients in Uganda found

that 64% of them had used traditional medicine since their HIV diagnosis, and usage was similar among those taking ART(397). Traditional medicine is rooted in spirituality and it is likely that people with HIV receive some spiritual care from traditional healers. Within Western healthcare in general, the spiritual aspect is frequently marginalised or neglected, due to HCWs' reluctance and lack of confidence(280). This may be less common in sub-Saharan Africa, where religious belief is very common (as shown above) and where a substantial proportion of health care is provided by religious organisations(398). In the qualitative interviews that formed part of the Public Health Evaluation alongside this cohort study, facility staff reported providing spiritual care including prayer with patients, spiritual counselling, arranging for a priest or spiritual leader to visit and helping patients come to terms with dying(363). Spiritual care was seen as a part of community and family life, so staff taught family carers to provide comfort and spiritual guidance to the patient.

In India a prevalence survey reported that 58% of patients were highly distressed by not being calm or peaceful(302). This could be equated with never/not very often feeling at peace, but it is actually measuring the level of distress caused by the problem, rather than its frequency or severity. The questionnaire was not provided, adding to the difficulty of interpretation, as the question phrasing can only be inferred from the reported answer. In any case, even if the tool was available, the cultural context might mean it was interpreted differently(382).

The majority of the literature on spirituality and HIV is based in the USA, where Ironson and colleagues have conducted a series of studies showing that following diagnosis, increased spirituality(269) and spiritual transformation are common, and predictive of improved well-being and survival(399). This research was conducted by retrospective interviews, asking people diagnosed many years previously to recall their emotions and spiritual condition at the time of HIV diagnosis. These methods are questionable. Psychology studies have shown that emotionally charged events are remembered with increased intensity but diminished accuracy(400). It is also known that memories can be altered and that a large proportion of memory is retrospectively constructed(270). Thus, interviews at many years' distance are not a viable way of gathering information about the experience of HIV diagnosis. In addition, spiritual transformation is a highly subjective

phenomenon, and important information is probably lost in its reduction to a quantifiable variable, ‘ST’. In Ironson et al’s work, ‘ST’ is normally associated with recovery from drug use, which in East Africa plays a very minor role in HIV transmission(1). Therefore the majority of the literature on spirituality and HIV diagnosis is either methodologically flawed or has little relevance to the majority of people diagnosed with HIV.

G.3.vii Difficulty obtaining help and advice

Problems obtaining help and advice are the most burdensome of all seven outcomes at diagnosis, with a median score of 4. As the area of greatest problems at baseline, this outcome has the most potential for improvement, and indeed it shows the best improvement over time (proportion of net change 38.3). Nonetheless, after three months over 20% of participants still report having had no help or advice in the previous three days. A great deal of unmet need remains, and proportion of net change declines steadily from month to month, suggesting that problems may continue to be unresolved.

Participants with limited physical function have fewer problems obtaining help and advice at baseline. Half of those with the worst physical function reported severe problems, compared to 58% of those with middle function and 68% of the best function group. This association disappeared entirely over time. The same association was observed with ability to share feelings, although it persisted over time. Physical function was scored by the HCW on the basis of observation. Patients with more evident, recognisable needs have fewer problems in areas that on social interaction. This could indicate that patients who appear well, and have best physical function, have difficulty getting their needs recognised as legitimate.

Education and wealth quintile are closely associated in this dataset. Wealth quintile was associated with the outcome in bivariate analysis, but this was almost certainly a product of confounding by education. The effect of education on ability to obtain help and advice is substantial and statistically significant, both at baseline and over time. There are several possible reasons for this effect. Limited literacy may

prevent full understanding of written health information. There may also be language barriers, as in Kenya and Uganda health information is often delivered in English, which is learned in school but rarely spoken at home. An unusual example of a language barrier was found during data collection. The questionnaires were translated into Luo, a minority language of western Kenya, but HCWs reported that they preferred to read from the Swahili version and translate mentally into Luo, because even though Luo was the first spoken language of themselves and their patients, they were not accustomed to seeing it in written form. Swahili and English were the languages of literacy. As well as these issues of direct communication, people with more education may find it easier to question and challenge health workers, using a shared vocabulary and understanding, or education may be linked to social status which empowers the patient to ask questions and elicits more respect from the HCW.

Only 6% of participants in Uganda reported low/no problems at baseline, compared to 23% in Kenya. Problems obtaining help and advice were notably more prevalent in Uganda, and this trend continued over time, showing the highest OR for any variable or outcome (3.30). The difference may have been partly caused by interpretation of the item. The full question is ‘Have you had enough help and advice for your family to plan for the future?’ It was designed to explore issues of bereavement support, legacies, making a will, looking after children, etc. In the systematic review, it was glossed as ‘information/tangible support’. A pioneering study in South Africa found that 11% of people with AIDS, unprompted, reported their worst problem was worry over who would take care of the children after they were gone(35). In a younger and more active population, facing the knowledge of a shortened lifespan but not imminent death, this question may have been interpreted differently. Cognitive interviews during validation showed that this item had the weakest face validity(256), as discussed under study limitations.

Without knowing exactly what participants meant by a need for help and advice, it must be assumed that they meant the needs reported most commonly in the literature. There is substantial evidence from Africa that people with HIV need material help and practical advice. The need for material support or advice is cited as a major reason to disclose HIV status(401), and the most frequently cited challenges to ART adherence are lack of food, transport and money(147). In

Rwanda, women recently diagnosed with HIV reported that they needed housing, employment, money, childcare and food, more frequently than healthcare(65). Nutritional support is important and inadequate(402). In a non-randomised comparison in West Africa, nutritional support at family level improved survival, adherence and CD4 count for people with HIV(403).

Over time, the majority of people report improved access to help and advice, but the proportion whose scores improve declines from 50.2% in the first month to 34.4% in the third, while the proportion reporting more problems increases from 17.1% to 26.0% at the same time. The fact that half of participants report a better score at M1 than M0 may be partially caused by a ceiling effect. For the majority of participants who scored the maximum of 5 at baseline, improvement or equality over the month were the only alternatives. Apart from this effect, it appears that efforts to improve patients' access to health and advice are less successful two or three months after HIV diagnosis than immediately after.

Participants on ART had fewer problems obtaining help and advice. These patients would have had a lower CD4 count than others, qualifying them for ART initiation. CD4 count was not associated with any outcomes cross-sectionally although ART was associated with three outcomes over time. This seems unexpected, as the main outcomes of ART are suppressed viral load and raised CD4 count, so outcomes improved by ART should also be affected by CD4 count. Also, access to help/advice unlike all other outcomes is not associated with physical function over time, which would suggest that it was not likely to be affected by an intervention aimed primarily at improving physical health.

The evidence indicates that it is not the antiretrovirals which improve ability to access help/advice, but some other aspect of ART. Patients on ART receive regular appointments and extra support and counselling(241), especially at treatment initiation, and this increased access to staff may have enabled participants to get the help and advice they sought.

Alternatively, perhaps the 'help' that patients wanted and said they had not received was ART. The results indicate that pre-ART patients also have palliative care-related problems. In Kenya and Uganda the CD4 threshold for ART initiation

has been raised from 200 to 350 cell/μl since these data were collected, following WHO recommendations. However, it is likely that pre-ART patients with a CD4 count above 350 will continue to have similar problems, since none of these problems were associated with CD4 count over time. In many settings pre-ART care is extremely poor, as shown by the very high loss to follow-up(158, 321). Scarce resources have been targeted towards the patients in most need, but better pre-ART care could help to redress and prevent problems, improving long term outcomes for patients at lower cost.

G.3.viii Total POS score

Although this thesis measures each problem separately and identifies its covariates, all seven problems are likely to affect each other, according to the theory of total pain. The seven palliative care-related problems described above can occur simultaneously and create complex needs for patients, which are more likely to require specialist care. The results for total POS score demonstrate that a minority of patients have severe, multiple complex problems.

The APCA African POS has rarely been analysed using a total patient score. Unpublished results from a natural experiment in Tanzania provide the only comparison. Participants were recruited if they had a POS score for pain or symptoms of 3, 4 or 5, the worst half of the scale. In the control group, the mean total POS score was 18.9 at the beginning and 16.4 after ten weeks(404). These scores are higher than those found in the newly diagnosed group whose mean score was 14.2 (95% CIs 13.7-14.6) at baseline, but this is to be expected, because the newly diagnosed cohort were representative of all patients whereas the Tanzania sample were specifically selected for higher than average pain and symptoms.

The total POS score has played only a minor role in this thesis. It has been used only in descriptive univariate analysis, to illuminate some of the relationship between the seven main outcome variables. Again, this was done to maintain a

patient-centred perspective and to remain as close as possible to the direct patient-reported outcomes rather than to alter them.

The validation of the APCA African POS calculated Cronbach's alpha for all ten POS items rather than the seven used here. The result was 0.6, indicating moderate internal consistency, as was expected from a tool that was not intended to be unidimensional. Usually, a Cronbach's alpha of less than 0.7 would indicate that it is not acceptable to create a summary score from the items. Confirmatory factor analysis of the UK POS also established that it is not a unidimensional scale, which is further reason not to use a single summary score as a statistical outcome(405).

On the other hand, although statistically the total POS score performs poorly, there are a number of indices with low internal consistency in clinical use. These tools usually have a very specific purpose. A score with low internal consistency is more likely to be used to identify those at risk and requiring additional assessment than to measure any specific problem. A common example is the five-item Apgar score, used one minute after birth to assess a baby's condition. Its components of heart rate, respiratory effort, colour, muscle tone and response to stimuli do not closely correlate with each other, but the Apgar score remains valid and useful because they are all indicators of a possible problem(406). Similarly the total POS score can be used to identify participants likely to have severe complex needs. The distribution of total POS scores has been presented here to demonstrate that severe complex needs do exist in this population of newly diagnosed patients and that a minority of them are likely to benefit from specialist palliative care. Given its limitations, the total POS score has been used descriptively only and is not an outcome in any multivariate analysis. The improvement in total POS score over time is expected, given that each individual POS outcome was shown to improve over time, and it does not provide additional evidence of improvement.

G.3.ixComparison between outcomes

Pain, symptoms and worry have similar score distributions at baseline, ability to find life worthwhile causes somewhat fewer problems, and lack of peace somewhat more. By contrast, ability to share feelings and lack of help and advice stand out clearly as the areas where severe problems are the norm, not the exception. While pain, symptoms, worry, peace, and feeling life is worthwhile are all individual conditions, the other two items have in common the fact that they are social and relational. The very high common and severe problems in these areas compared to others suggest that people newly diagnosed with HIV are likely to feel isolated and alone. The difference may reflect a distinction between personal wellbeing and social integration

At baseline, three outcomes (peace, feeling life worthwhile, help and advice) have better scores in Kenya. Over time, five outcomes (the same three plus pain and worry) have better scores in Kenya, and no outcomes are better in Uganda. These associations are independent of wealth quintile, although participants in Uganda are poorer than those in Kenya. Country is the covariate most strongly associated with the psycho-spiritual outcomes peace and life worth, and has an even stronger association with the more practical and social outcome of help and advice.

G.4 Generalisability of findings

The findings presented here represent a substantial contribution to the literature on patient-reported problems at HIV diagnosis. The rest of the evidence as identified in a systematic review was very limited. Eleven studies took place in low-income countries, but five of these recruited only pregnant women(65, 79, 105, 289, 294), and three more were chart reviews of inpatient with a comorbidity (286, 296, 297). Six studies came from middle-income counties but their quality was very variable(260, 287, 301-304). Finally 17 studies were conducted in high-income countries, but three of these recruited pregnant women only(285, 288, 295), three recruited people with recent seroconversion(136, 292, 293), and a further seven took place before the development of HAART in 1996(263, 290, 291, 305-308). Most of these are not representative of a contemporary population newly diagnosed with HIV. Also, none of the studies in the systematic review used a multi-centre design, so any idiosyncrasies of the study site would not have been apparent and would have affect the results. By contrast, the data used in this thesis came from consecutively recruited newly diagnosed people presenting for care in two countries and represent the most realistic and representative sample ever presented.

The paucity of research in the area make these findings valuable and relevant beyond the context in which they were collected, but care must be taken not to extend their application too far, simply for lack of alternatives. For example, the West African pandemic is very different from East Africa (more concentrated, lower overall prevalence, and presence of HIV-2(16)), quite apart from the linguistic, cultural, economic and situational variation. However, evidence of multidimensional needs at HIV diagnosis in West Africa currently comprises one cross-sectional checklist of physical symptoms(303) and one quality of life questionnaire with 56 Air Force recruits(287), both from Nigeria. Multidimensional problems are virtually unknown and evidence of change over time is completely absent. Similarly, HIV diagnosis from a patient-centred perspective in South America is a mystery apart from one chart review of symptom prevalence in Brazil(260). The findings presented here from Kenya and Uganda increase the probability that people in other settings experience severe and highly prevalent multidimensional problems in

the first months after HIV diagnosis, but they by no means compensate for the lack of quality patient-centred evidence from those settings.

The eleven facilities in the study were selected from all those in Kenya and Uganda receiving PEPFAR Care and Support funding. The largest facilities from a random sample were chosen in each country, the reason being that facilities hosting the study needed to have sufficient patients and staff capacity. Previous findings as part of the evaluation showed that the larger facilities offered a wider range of care(346, 347), although quality of care was not measured. Therefore, it is likely that these eleven facilities provided better multidimensional care better than that available to the average patient. The improvement in outcomes seen in this sample is probably a best case scenario.

The analysis presented here did not take account of differences between sites, or to put it another way of clustering by site. This was partly because the sites differed greatly in the number of participants recruited from each, with one site represented by only three participants. Adjustment for clustering would give too much weight to small sites. I could have dropped the smallest sites from the analysis but the general problem would have remained.

G.4.i Generalisability between Kenya and Uganda

Participants were consecutively recruited with very few refusals, and therefore they are representative of patients newly diagnosed with HIV who seek care at the eleven facilities where data were collected. The eleven sites were the largest (in terms of annual patient numbers) in each country from a stratified random sample of PEPFAR-funded facilities. Large facilities were selected so that they would have the capacity and resources to host the study. Very generally, larger sites deliver a better quality of care, especially in resource-poor contexts where smaller facilities are less likely to have necessary staff, equipment or drugs. Phase 1 of the PHE found clear associations between facility size and the range of care delivered, although care quality and outcomes were not recorded(346, 347). Thus, these facilities differ in known ways from the majority of PEPFAR-funded sites, and differ in unknown ways from health facilities in Kenya and Uganda which are not funded by PEPFAR to deliver multidimensional care and support.

Physical function scores were generally good, with 70% of participants reporting the best possible ECOG score of zero, but multidimensional problems were highly prevalent. Previous studies have often recruited populations with advanced disease or AIDS(298), but these findings show that multidimensional problems are also common earlier in the HIV disease trajectory. The sample was 62% female, which is a normal gender ratio for a group of people receiving HIV care. Men are at slightly lower risk than women of HIV in Africa, but the main reason for the discrepancy is that men are less likely to have an HIV test or to present for care(16).

The extent of difference in outcomes between Kenya and Uganda was unexpected. It is unclear whether these national differences are caused by cultural interpretation of the questions, socioeconomic background, difference in care provision, or some other factor. Problems with symptoms and worry were similar at baseline but the countries diverged over time. The only common trend to all national difference was that problems were always more severe in Uganda than Kenya. The fact that Kenya and Uganda, neighbouring countries with close cultural and economic ties, produce such different results casts doubt on the representativeness of findings beyond these two countries. However, the systematic review shows that evidence of problems at HIV diagnosis is extremely limited in quantity, quality and representativeness, especially in its application to African outpatients. The findings presented in this thesis are more likely to be appropriate to outpatient settings in the rest of Africa than any data previously published.

Kenya is a more developed country than Uganda, with a higher life expectancy, degree of urbanisation and Gross Domestic Product(20), but it also has a greater proportion of its population living below the poverty line, showing that the extra income is not equally shared. It does not seem likely that the differences observed between Uganda and Kenya were caused by economic factors. The outcome most affected by country – access to help and advice – was not associated with wealth quintile at all, and neither were worry and difficulty finding peace which were both more prevalent in Uganda over time. On the other hand, pain was closely associated with wealth quintile but not with country.

The strongest associations with country were seen for difficulty finding life worthwhile, finding peace, and accessing help and advice. The first is highly dependent on cultural expectations of what gives worth to life. The second attempts to define the contentious and culturally variable concept(394, 407) of spiritual wellbeing. The third outcome was shown in cognitive interviews to be the most problematic item, with varied interpretations. Thus it appears that the differences between the two countries may have been caused by cultural and linguistic interpretations of the items. The four translations of the POS used in this study were not validated after translation. If they had been, it would now be easier to estimate how much difference between Uganda and Kenya is real, and how much is a product of the questionnaire.

On the other hand, translation errors would be expected to be random; either country might end up with a higher prevalence of problems. In this case, Kenya always has fewer problems in every case where there is a difference, which argues for a systematic bias such as a different patient demographic or better care.

The difference between Kenya and Uganda also implies that there would have been clustering by site. Site occupies a middle level between country and individual. Since there were only five sites in one country and six in the other, the national difference could have been caused by extreme results in one or two facilities. The effect of facility-level clustering could be examined using multi-level modelling, to identify whether structural factors are associated with the outcomes.

G.4.ii Generalisability to high-income countries

The extent to which these results can be generalised to the rest of the world depends partly on how much the experience of being HIV positive is common across boundaries and cultures, and this is uncertain. Differences between the experience of HIV in a low-income and a high-income country include risk factor for infection, background health status, and availability of treatment and health care resources.

1. Risk factors for infection

In Africa the main routes of infection are heterosexual sex and vertical transmission. As a result, a third of people with HIV are children aged under 15 and 60% of the adults are women(16). In high-income countries where vertical transmission is very rare and the epidemic is much more concentrated, the majority of people with HIV are men, and women with HIV are disproportionately likely to be IDU or sex workers. These populations have specific health needs of their own which are not typical for all women. The natural history of HIV in children is much less well known than it is for adults. Children are also at higher risk than adults of morbidity and mortality from enteropathic infections and diarrhoea. Therefore the different risk factors for infection lead to HIV positive populations with entirely different demographic characteristics, health risks, and prognoses.

2. Background health status

Even without HIV, life expectancy would be lower in Africa. When the initial expectations of a healthy life are different it is not simple to compare the relative impact of HIV between settings. The incidence of many infectious diseases is much higher in Africa, due to warmer climate and limited access to health services. A person with HIV is more likely to encounter someone with active TB and therefore more likely to have HIV and TB co-infection, with increased symptom burden(408). Several large-scale seroconversion cohort studies in Uganda found increased all-cause mortality risk(409), rapid progression to WHO stage 2 and high symptom burden compared to high-income country cohort, but CD4 counts appeared to be within the same range(357, 358). The reason was that the common indicators for WHO Stage 2 and 3 (weight loss, prolonged fever, pulmonary TB, skin problems and bacterial infections) were highly prevalent in the HIV-negative population(357, 410). The question then arises whether HIV progression was really accelerated or not. If the outcome is morbidity and mortality, HIV progresses faster in Africa. If the outcome is CD4 count then there appears to be little difference. From the patient-centred perspective, the former is more accurate, since morbidity directly affects the patient as CD4 count does not.

3. Health care resources

The time between infection and diagnosis is on average longer in Africa, thus newly diagnosed people are more likely to present with advanced illness. Delays are caused by limited access to testing facilities and to health care workers who might recognise HIV symptoms. ART services are expanding rapidly but in 2008 only 44% of those who needed treatment in Africa were accessing it(29). Life expectancy, quality of life and symptom prevalence are all affected by ART, so it is not possible to establish the contribution that universal access makes to the better outcomes in high-income countries.

4. Stigma

Societal response to HIV affects the experience of living with it. Since lack of social support is a risk factor for depression, and depression is a risk factor for accelerated disease progression, stigma may actually limit life expectancy. In this study, the areas of greatest burden are inability to share feelings and a lack of help and advice for the family, both of which are largely social problems.

5. Biological variation

Some argue that the progression of HIV disease is faster in Africa than in high-income countries after accounting for all other confounders, due to either physiological differences in immune response of the people with HIV, or a more virulent strain of virus(409).

The demographic features and disease burden described above for Africa also affect black Africans with HIV in high-income countries. In the UK, black Africans on average present for an HIV test with more symptoms than people of other ethnic groups (257). Black women with HIV have fewer lifetime sexual partners than white women but are nearly always infected through sexual intercourse, and are more likely to have AIDS and TB at diagnosis(411). These findings demonstrate that the division between low-income and high-income country HIV profiles is not clear-cut.

Several of the factors discussed above are in a state of change, and the relative contribution of each to patient experience of HIV diagnosis is unclear.

G.5 Study strengths

This is the first known study of multidimensional problems in newly diagnosed African outpatients, who comprise the majority of people diagnosed with HIV. It makes a substantial contribution to the body of evidence regarding HIV diagnosis. It is the largest and most methodologically rigorous prospective study ever published on HIV diagnosis, and it presents the most reliable evidence yet obtained for the experience of HIV diagnosis in any population, and from any scientific field. The study's quality rests in the representativeness of the sample, the suitability of the tools and the statistical analysis.

The sample is recruited consecutively with few refusals and is thus representative of people attending for care at eleven public HIV care centres in two countries. It is very large, consisting of 438 people interviewed up to four times. All participants were recruited within two weeks of HIV diagnosis, which has scarcely been attempted since the earliest studies of reaction to diagnosis in the 1980s(263). Thus the dataset is highly original and probably unique. Building contact between the person with HIV and health care services is easiest and most effective if done at HIV diagnosis; easiest because the person is already in contact with a health worker at that point, and most effective because it is as early as possible. Therefore, this sample closely represents the patient group relevant to care.

This is the first longitudinal study of outpatients in a low-income country and the first study anywhere to collect data more than three times within six months of diagnosis. These areas were identified as lacking from longitudinal research in the systematic review. Completion rate is good and LTFU is low. Multidimensional outcomes are analysed and compared, whereas previous studies have usually measured outcomes in only one or two areas. The outcome tool was developed for the purpose and validated in the settings, which improves the reliability of findings. Data were collected prospectively and the period of recollection is only three days, limiting recall bias, which is a risk in studies of emotionally charged events(270). The outcomes are centred on patient experience rather than latent variables. The data were cleaned and checked according to best practice.

The study used novel longitudinal analysis techniques which have never been employed in any patient-centred study of HIV diagnosis. As a result this is the first and only study to adjust for variation between individuals when analysing change over time. Four different methods of analysis were used, each selected to best fulfil one of the objectives. Measures were taken to prevent ‘data dredging’ and the production of spurious findings. A detailed analysis plan was written in advance, and statistical tests were kept to a minimum. Conservative methods were used, for example analysing the ternary POS outcome scores at ordinal rather than categorical, which halved the quantity of output but increased power.

Only three studies of outpatients at HIV diagnosis in low-income countries were identified in the systematic review of HIV diagnosis. One is a retrospective study of patient records in Haiti, with unclear methodology(300). Another is a study of AIDS patients, who are not typical of the average person at HIV diagnosis(298). The third investigates predictors of HIV status disclosure(299) and views the newly diagnosed person as a potential vector of disease, rather than a patient in need of care.

In line with the study aim, findings are clinically oriented and patient-centred. POS items were chosen as the outcome because they are directly patient-reported without alteration. As much as possible, POS items have been analysed individually resisting the use of combination or overall scores, to maintain patient-centredness. The total POS score has been used only in univariate analysis to show the existence of patients with multiple complex needs. For all outcomes, univariate data are presented before any more complex analysis is undertaken, and the first section of the longitudinal analysis uses a readily interpretable technique, proportion of net change, to make the data more accessible to clinicians. As another example of clinical relevance, the first appearance of the patient after diagnosis (T0) was consistently used as the baseline in longitudinal analysis rather than the day of diagnosis itself, because care could only be delivered from T0 onwards and so linking back to diagnosis would have set up unreachable targets for care.

Three questions are of particular interest for clinicians: is it possible to predict who will have severe problems at diagnosis, whose problems increase over time, and

whose problems recur? The multivariate analysis of risk factors at baseline answers the first of these questions, but it uses all the data. Since for most of the outcomes moderate problems are more prevalent than severe ones, risk factors for moderate problems will tend to overshadow those for the most severe, even with an outcome imputed as linear.

The multivariate analysis of change over time goes some way towards understanding those whose problems improve the least, which certainly includes the patients whose problems get worse over time. However, an alternative method would have been to identify these patients at the start and compare them to patients who recover, essentially using a case-control design. This could be a more appropriate method given that for several items only a small number of participants report scores 4 and 5. Further work could adopt this approach.

G.6 Study limitations

G.6.i Study design

The decision to investigate palliative care-related problems of newly diagnosed participants as a group was not made until after the beginning of data collection. Thus the study is a secondary analysis, albeit one in which the new analysis is very close to the original purpose of the study and conducted by the same person. I drafted the aims and objectives were drafted before any primary analysis had been undertaken, so nothing was known of the characteristics of the newly diagnosed population. Also, I was heavily involved in the study design and conduct from its inception. I designed the questionnaire packs, wrote training material, built the database, trained research assistants and HCWs, monitored data entry, and was responsible for statistical analysis and writing reports. Because of this, I was very familiar with the dataset and able to contextualise it, having the benefits of primary analysis.

The dataset is very large for a palliative care study, but the use of multivariate analysis with up to seven independent variables led to some very small subgroups. In particular, the group with the worst physical function is very important (since they have greater needs in almost all areas) but numbers only 30 people. It would have been difficult to oversample this group since the design used total consecutive sampling of new patients. Recruitment at smaller health facilities, closer to patients' homes, might have resulted in a greater proportion of people with restricted function. Access to the larger health centres with a wider catchment area could require more investment of time, energy and money, which may have biased the study against recruitment of poorer, disabled or more severely ill patients.

Each of the eleven facilities recruited between 100 and 125 participants to the PHE, but the number per facility who were newly diagnosed varied from three to 80.The facilities themselves were selected for their suitability for the PHE, as the largest six per country of a random sample of PEPFAR-funded facilities. Some participants had tested positive at a community health centre several days earlier,

been referred to the larger PEPFAR facility and then been recruited to the study. It was for this reason that the inclusion criteria allowed participants to be diagnosed up to 14 days prior to recruitment, as this visit could well have been their first opportunity to receive HIV care. An ideal sample would have recruited from primary level clinics which conducted frequent HIV tests, and would have recruited participants on the day of HIV diagnosis.

Data collection was performed by HCWs employed by the health centres, who were trained and supported by independent research assistants from APCA. This is a possible source of bias, as HCWs could be motivated to show that their facility was successfully managing problems, especially since the main purpose of the PHE was to evaluate services for a major funder.

There was considerable change over time during the study, which was especially rapid in the first month. It would have been interesting to collect data more frequently. There is evidence in the literature that change in psychological state in the first days after diagnosis can be very rapid(263). The POS describes only a period of three days and was designed to be sensitive to change in short period of times. The systematic review identified no longitudinal studies with more than four data points. This limitation makes it difficult to study trajectory or to model non-linear data.

Only adults aged 18 and over were included in this study, because the APCA African POS is not validated for use in children. The majority of under-18s are diagnosed in infancy, and for this group the experience of diagnosis is of course very different. Clinical guidelines encourage gradual disclosure to the child, in stages as appropriate to their age and understanding, but without unnecessary delay(412). Those diagnosed in adolescence have a situation more comparable with that of the adults in this study (i.e. an abrupt diagnosis and initiation into care). In HIV prevalence surveys, adolescents aged 15-18 are usually grouped together with adults(16), but their problems and needs at diagnosis may well be unique, and they should be studied separately rather than simply included with adults to enable delivery of appropriate care. A paediatric POS to enable research in this area is in development.

The study is representative only of people who have a health care consultation within two weeks of HIV diagnosis, either because they were diagnosed on the same day or because they were referred from a different testing facility and kept the appointment. They do not reflect the experience of those who delayed seeking health care after their diagnosis. In Cameroon, a retrospective survey of 3151 outpatients with HIV found that 43% delayed their first medical consultation for more than a month after their diagnosis, with 15% delaying for more than six months(266). In this study, the people in contact with care services reported very severe problems, above all in accessing help/advice and sharing their feelings. It is likely that these problems would have been even more severe for people who did not receive any further care in the two weeks or three months following their diagnosis, while those having monthly appointments reported all the problems observed here.

G.6.ii Outcome tool

The outcome instrument, the POS, is multidimensional, whereas a typical QoL instrument aims to be unidimensional. Each question is aimed at eliciting information about a different area of need according to the WHO definition of palliative care(11). Multiple questions on a single topic are avoided in order to keep the tool as brief as possible, which results in a low Cronbach's alpha(256). For this reason, all analysis has presented the seven items separately before creating a combined score. It is also clinically more useful to analyse by item.

The tool was not revalidated after translation. The scores in the two countries differ most for the outcomes of peace and feeling life is worthwhile, which are difficult to define. Some of the difference between countries may be caused by cultural or linguistic understanding of the question. Even when back-translation ensures that a questionnaire is exactly the same in the new language, the concepts it uses may not be translatable.

The item 'Have you had enough help and advice for your family to plan for the future?' in particular caused problems and may have been misinterpreted.

Cognitive interviews during the validation of the APCA African POS found that this question had the poorest face validity. Of 46 responses, 13 showed comprehension difficulties, although detail is not provided on how participants interpreted the question(256). Clearly the question does not mean the same thing to all participants. Therefore, although the responses show that a vast need exists in this area, it is not clear exactly what that need consists of or how it should be met. More specific information is needed to understand the nature of patients' problems. Qualitative methods might be a more appropriate way to research this area, since it is only possible to develop a valid questionnaire once a shared meaning is established.

The version of the POS that was used in validation included text phrases only for the two ends of the scale, numbers 0 and 5(256). For example the first question, 'Please rate your pain in the last three days' asked patients to rate their pain 'from 0(no pain at all) to 5(overwhelming; the worst pain you can imagine)'. In piloting for the PHE, HCWs reported that patients found it difficult to match their experience to a number and they would prefer to select from a list of phrases. The POS response sheet was therefore modified, so that the possible answers for the pain question became '0(not at all), 1(slight pain), 2(moderate pain), 3(severe pain, interferes with activities of daily life), 4(very severe pain), 5(overwhelming; the worst pain you can imagine)'. These phrases were translated and back-translated into the various languages used in the study. The consequence of this modification is to force a certain interpretation of the scale upon the participant. I have not used these phrases in the thesis as they were not validated.

In this thesis, the item scales have been presented alongside each other as though they were comparable. While each item is separate from the others, there is an underlying assumption that they represent the application of the same 0-5 scale in different areas. The same analysis is applied to each of the seven items. In Part A, for instance, I interpret the results to mean that the need for help and advice is the area of most severe problems because the proportion to report a score of 5 was highest for that item. This assumes that the different items can be compared with each other. In the validated POS, each item was anchored at each end,. The best possible score was always 'no problem' (phrased as 'no pain', 'not at all', 'able to talk freely', 'all the time, 'as much as wanted', according to the question). The worst

possible score was ‘overwhelming, ‘all the time’, ‘not at all’, or ‘none’. They described extremes and therefore they could be considered comparable, although the problems they described were very different. The lowest score always meant no problem at all and the highest always meant an all-consuming problem.

With the addition of new intermediate text phrases, the issue of comparability was confused. For example, a score of 3 can mean ‘severe pain’, ‘worried a lot of the time’, ‘been able to share feelings occasionally’, or ‘had help and advice for a few things’. It is unclear whether all these situations should be considered as equal, such that the percentage of participants scoring 3 or above in each area could be evaluated usefully. Without the text phrases, participants would have been assessing their own situation for each item as ‘3, if 0 is no problem and 5 is the worst possible problem’, which might result in a fairer comparison between items.

Feedback from research assistants in the field indicated that participants preferred text phrases to numbers. To use them, a POS with text phrases would need to be tested and validated. There are plans also to develop and field test a POS ladder, allowing participants to point at a certain position on the scale, similar to a Visual Assessment Score (VAS).

It is a disadvantage of secondary analysis that the outcome tool cannot be altered or refined. The POS is ideal for the patient-centred aim of this study but some of its features, such as brevity, are less advantageous in this population of relatively active young adults than in a group of terminally ill hospice patients for whom the tool was in part designed.

Alternative outcome tools

The POS is patient-centred. The same instrument is used in both clinical care and research, demonstrating that its responses are meant to be useful at the patient level, whereas some tools are designed to be averaged over a population and give distorted results when applied to one person. It is not disease-centred; problems recorded on the POS do not have to be caused by HIV. Nor is it centred on the HCW; problems need not be manageable. The POS measures holistic, patient-identified problems.

Asking about specific symptoms could have elicited more information than asking about symptoms in general. Dr Hellen Kariuki at the University of Nairobi reported that patients expect fatigue and tiredness to be inevitable in illness, and so they do not complain of these symptoms (personal communication). In the USA, patients with HIV report three times as many symptoms as their clinicians do(54), and the patient-reported symptoms correlate better with clinical outcomes(54, 413). It would have been interesting to compare symptom prevalence results with the literature. The MSAS would have been ideal. It is a validated instrument(414) and has been used in populations with AIDS in Uganda(298) and the USA(46) and on men receiving ART in the UK(10).

The PHE also made use of the MOS-HIV, a culturally adapted(66, 415) QoL instrument and the most widely used in HIV, notably as a secondary outcome in ART trials(416). I chose not to use the MOS-HIV subscores or combined scores as outcomes in my analysis. This was because the aim was to be patient-centred and to adhere as closely as possible to the patients' self-reported experience, by measuring palliative care-related problems at diagnosis, which the MOS-HIV is not able to do. Basic information on the prevalence and severity of problems in different areas is required before it is appropriate to explore latent variables or to summarise problems into combined scores.

G.6.iiiMissing data

I made the decision not to use imputation or Heckman-type selection modelling(417) in this thesis to adjust for missing data. Instead I analysed observed data only. Either choice involves assumptions. In this case I made the assumption that the unobserved data was not informatively different from the observed data.

The analysis of missingness patterns for Part C of the analysis revealed that the total POS scores at baseline of people who later had missing data were on average higher than the mean score for people with a complete data record. The effect was not significant (the 95% confidence intervals overlapped), but this was partly because the groups with missing data were small and so their confidence

intervals were quite wide. If the groups had been of similar size, their confidence intervals would not have overlapped. Therefore it would have been more conservative to have used either Heckman selection or imputation to adjust for missing data and the lack of such adjustment is a limitation of the thesis. Future work using this dataset will adjust for missingness. However, as I explain below, there is reason to think that missingness will not substantially affect the results and will tend to underestimate rather than overestimate problems.

The proportion of net change analysis shows that POS item score at one time is associated with score at a later time. If it was not, the distribution of change values would be flat, rather than parametric. Therefore the missing POS sores at later time points are likely to have been on average higher than the observed scores, and thus data should be considered MNAR. Participants who dropped out of the study or missed a data point probably had more multidimensional problems than those who remained. As a result, the improvement in scores over time has been inflated, some of it being caused by bias due to LTFU.

The results presented here tend to underestimate the prevalence and severity of multidimensional problems. Multidimensional problems are worse and more common between one and three months after HIV diagnosis than has been reported. This attrition bias is known. An additional an unknown selection bias is also likely to have occurred, because the sample does not represent those individuals who did not attend for care within two weeks of their HIV diagnosis, who may represent the majority of people diagnosed. In Johannesburg, 85% of patients with CD4>200 did not return for their CD4 test result within six months after HIV diagnosis(145), and in Durban 31% were LTFU within three months between their HIV test and CD4 test(157). These two biases are similar. Every adult who presented for care within two weeks of diagnosis was recruited, with very low refusal. The main reason for loss to follow-up at later time points was failure to appear at the health facility, therefore representing not only LTFU from the study but also from clinical appointments. The sample represents patients who are actually seen by health care workers and in that sense it is of direct clinical relevance. The patients LTFU after their first post-diagnosis appointment and the much larger group who are LTFU before that probably have an even higher burden of multidimensional problems which are not being addressed.

In Part D of the analysis, the logit models are less affected because all observed data points are used, rather than only those within specific time periods as for the proportion of net change in Part C. Form this full dataset only 13.8% of observations were missing. A common rule of thumb for the effect of attrition on validity is that less than 5% LTFU probably causes little bias but more than 20% poses serious threats to validity(418). For values in between, the effect depends on other factors including the study design and analysis methods. The methods used for Part D were chosen because they are robust to informative missingness(334) The risk factors for multidimensional problems over time described in Part D are mainly the same as the risk factors for multidimensional problems cross-sectionally described in Part B, which had no missing data. Therefore the results in Part D are probably less affected by attrition bias. Where there is an effect, it will tend to inflate the extent of change over time.

G.6.ivWealth Index

Relative poverty undeniably has considerable impact on access to care and on health outcomes, but it is not a single, objective quality and there is no gold standard way to measure it. The DHS method used here has been validated(333) and is one of the most widely accepted methods used in the Demographic Health Surveys project in collaboration with the World Bank. In this study, the basic Wealth Index questionnaire was used without alteration. It is possible to add additional context-specific assets to the list, if home construction, ownership of goods, and quality of daily resources (water, sanitation, fuel) are expected to fail to pick up important information. Not enough was known about Kenya and Uganda to tailor the questionnaire to the context.

Variables with the highest loading on the Wealth Index in principal components analysis were, in order: an earth floor (negative), owning a television, owning a flush toilet, owning a refrigerator, a house of mud and brick (negative), owning a mobile phone, using well water (negative). Rare items which are strongly associated with poverty are likely to have high loadings. The Wealth Index has been criticised for a rural/urban bias. For example, a corrugated iron roof usually

scores ‘better’ than thatch because the poorest members of the population have thatched roofs. This can lead to a situation where a slum has a higher score than a village, although the quality of life and health status of the slum dweller may be lower(419). Related to this, it is not clear whether the difference between Kenya and Uganda is representative of the two countries. Kenya has a higher GDP than Uganda and its facilities in this study are more urban (see Appendix C).

The score is called a Wealth Index rather than a poverty index. The entire cohort is relatively poor, with only 16% having indoor piped water, 12% a household car and 10% a flush toilet. I have referred to some participants as wealthier than others but it might be more appropriate to say that they are less poor. Even within an environment of widespread financial constraints, the very poorest participants have the greatest needs.

G.6.v Data accuracy

In the PHE, data management was good, using coded questionnaires and a matched database, with double entry and validation. These techniques were not possible for the collection of CD4 count data, which were extracted from patient records. It was not practicable to do this twice and so data collection consisted of a research assistant copying CD4 counts and dates by hand onto a spreadsheet. Mistakes detected during cleaning included duplication, reversal of month and day, repetition of CD4 count, and writing the current year by mistake. Only errors which are impossible, systematic or very unlikely could be identified and checked. The CD4 results are the weakest point of the dataset and it is partly for this reason that I have made little use of them.

Other errors may also exist. Around 20 people in the original sample reported they were newly diagnosed but their patient records showed a CD4 count predating their supposed HIV test, therefore they were not included. All available information on dates (date of CD4 count, of registration, of data collection and entry, of WHO staging, etc.) was cross-checked to seek out other errors and whenever there was doubt over a person’s eligibility for the sample, they were dropped. In other words, I

attempted to minimise the number of false positives by accepting the loss of some false negatives (participants who might have been newly diagnosed but whose information was lacking or inconsistent). Even so, it is possible that this sample of 438 includes individuals who were actually diagnosed HIV positive long before recruitment. However, the sample size is so large that a small number of false positives like this would be unlikely to influence the findings.

In a large clinic in South Africa, the most resource-rich country in the region, the majority of people who come for VCT and are diagnosed HIV positive do not enter care(145). The connection between testing and care is frequently and perhaps repeatedly broken. As people with HIV negotiate the barriers that prevent them accessing care, they may return to the same health centre or a different one, and re-test. Therefore the sample of 438 people within two weeks of diagnosis in this study may not be newly diagnosed for the first time. In terms of patient-centred health care provision, this is not a priority. The group may not entirely consist of people who have just discovered they have HIV, but it is representative of the patients who require from-diagnosis care. These patients were recruited at the point of diagnosis and that incident is their link to health care. If the link has been broken in the past, all the more reason to address their needs on this occasion.

In the UK, there have been cases of people concealing a previous HIV diagnosis and treatment, who were identified by resistance to ARVs (420). In the absence of a robust referral network, it would be possible for people to register more than once and receive a double script of ARVs, despite efforts to prevent this. A lost connection to care is probably the more likely scenario.

HCWs reported that many participants were diagnosed at small health posts or mobile testing centres, and referred to the participating facility for care. An unknown proportion of newly diagnosed people did not follow up this referral within two weeks of diagnosis and hence were not included in the study sample. It is likely that the individuals who did not attend for care after their diagnosis, or who delayed their care, had more multidimensional problems than those who went within two weeks.

G.6.viAnalytic methodology

Loss to follow-up was low, with 75% of participants (n=325) completing all four time points, but the 25% who left the study are likely to differ from those who stayed, possibly in ways that would affect the findings. In setting the criteria for Part C analysis, which required data to fall within specific times from diagnosis, I reduced the number of participants with four valid observations to 185. This was a substantial loss of data. The 185 may have been different from the total 325 who completed four observations, or from the total 438 who began the study.

Throughout the analysis plan I used $p<0.05$ as the threshold for retention of independent variables, as is standard practice, but the choice is arbitrary. There is nothing inherently important about $p<0.05$. In the analysis of variables associated with symptoms, country had a p-value of 0.052 until age was removed, when it reduced to 0.049. The change was minute, but because it crossed the significance threshold of 0.05, country remained in the model as a predictor of symptom burden. I discuss the OR, standard error and confidence intervals in my interpretation of the results, rather than focus solely on the p-value.

The number of statistical tests performed increases the risk of Type II error. I took several precautions to reduce this risk. I analysed change over the full time period before breaking it down by month and if there had been no overall change over three months I would not have proceeded further. In Part D, every independent variable is analysed against every outcome, which produces 56 separate statistical tests. However, these are used only to select variables to take forward to multivariate analysis. I do not draw conclusions from the univariate results as the risk of Type II error is too high. Most of the analysis in part B is process rather than outcome. It is used to make decisions regarding the structure of the final model.

The twelve facilities selected for the PHE (of which eleven recruited newly diagnosed participants) were selected based on size. They are not typical of HIV care centres in Kenya and Uganda or even of PEPFAR-funded centres. The PHE found that larger facilities offer a wider range of care, although they are less likely than community-based services to offer social care(346, 347). It is a limitation of

the results that all participants were recruited from facilities that had this feature in common.

The ordered categorical variables wealth quintile, age category and physical function were used as though they were continuous. The distance between one stage and the next is assumed to be constant. This is fairly common practice in regression models, and it is the reason why, in the graphs in Part D, the lines for each quintile are always an equal distance apart. An alternative method would have been to use dummy variables, one for each possible value. This would have increased the number of independent variables relative to the sample size, and possibly made the models unstable so that they did not resolve. It would also have raised the possibility of finding results that did not form a trend, such as a tendency for middle-income people to have more problems than both the wealthier and poorer quintiles. Age category, wealth quintile and physical function are all categorical representations of an underlying linear variable. I considered that non-trend results were more likely to be artefacts of the analysis. Given the big sample size, strong statistical power, and number of outcomes, the risk of Type II error was high and so I tried to minimise it by using single independent variables instead of dummies.

In the multivariate longitudinal analysis, the six-item scale was transformed into a binary one, with consequent loss of detail. It is possible that a high level of problems might have very different risk factors, consequences and impact on quality of life from a moderate problem. In fact, the multivariate cross-sectional analysis found this to be the case, in some areas, but not many. For the most part, the same risk factors were associated with the outcomes in both strata, and also over time when stratifying was not used.

Age categories were 18-25, 26-40 and 41-59, with the aim of detecting a relationship between lifetime experience of HIV and perception of stigma. The two variables associated with age were difficulty finding peace and finding life worthwhile, which are influenced by perception of HIV, but it is not possible to distinguish the cohort effect of experience from the age effect of maturity. This is a frequent problem when trying to ascertain the effect of age on an outcome. Using three age groups was appropriate, but it would have been a more efficient use of

the data to divide the group into approximate tertiles rather than have one group bigger than the other two combined.

The demographic and clinical questionnaire included a closed question on ‘reason for attending facility today’, and an open text box for ‘place referred from’. This information could have been very useful in understanding whether symptoms or worries motivated people to have an HIV test. Unfortunately, the questions were not sufficiently covered in training, results proved to be highly variable between facilities depending on how they were interpreted, and the data were not usable.

The logit models in Part D may appear to overload the data. For example, the model in Figure F-16 contains a theoretical 60 categories, of which seven are empty. In fact, the technique maximises power because all 1511 observations contribute to the development of the model and the categories are population-averaged, so they do not rely solely on the data within that category.

The proportion of net change method reduces the complexity of data and does not take full advantage of the longitudinal dataset. It was done because no longitudinal methods allow for a skewed, non-parametric, short-scale ordinal variable such as a POS item, and also because it is a simple, replicable technique and an example for other analysis, as discussed in Section G.7. In longitudinal analysis, the problem was resolved by turning the ordinal variable into a binary one, with consequent loss of information. In order to retain the detail of the outcome measure it was necessary to lose the detail of the time measure, and group time into categories (M0, M1 etc). This reduced the sample size, as time points which did not fit into a category were dropped, but the very large size of the sample meant this could be an acceptable trade-off.

It is not possible to distinguish unmet need from absence of need for care, and this is particularly noticeable with ART. While all eleven facilities had ART, funds and supplies could be limited, and are limited and in order to maintain therapy for existing patients, some facilities would halt ART initiation for a time. Combined with the literature showing that many patients eligible for ART are not enrolled(157), it is likely that some people in the study were suitable to begin ART, but not receiving it. Recent CD4 count data were missing for many patients, and there is no

guaranteed method to determine need for ART from the data available. The study is a representative sample of outpatient care, in that some patients do not need ART, some are taking it, and some are in want of it. Three outcomes were associated with ART (and one more just missed significance) but it is not possible to separate the non-ART group by need.

I did not investigate correlations between the seven outcomes, or model the effect of one outcome on another over time. There were two reasons for this. Firstly, there would be a great many possible models, with a correspondingly high probability of spurious results. Secondly, correlation is very likely to occur and this would not prove causation or even a non-confounded association. Intrinsic to the philosophy of palliative care is the concept that the different dimensions are interconnected and that problems in one area cannot be treated effectively without addressing other areas too. Correlation between pain and worry, or peace and finding life worthwhile, is so likely to happen that it is not a good use of a statistical test, because the null hypothesis is probably untrue. A factor analysis of the results would be a logical next step to identify the strength of associations between items but it was beyond the scope of this thesis.

In longitudinal analysis, I chose to use the population-averaged approach rather than the individual-specific approach, even though personal trajectories and the variation between individuals are of great interest in palliative care. This is the first prospective multidimensional study of newly diagnosed outpatients in Africa, and has no hypotheses for lack of evidence to support any. In pioneering research such as this, population-level analysis is more appropriate, which can later be developed to explore the variation and complexity within the major trends found here. I also carried out some individual-specific longitudinal logistic regression (using fixed effects), and found, as is typical(338), that the results were quite similar to those presented here but a little more extreme. This analysis is not presented here because it does not contribute further to an understanding of the data.

G.7 Methodological contributions

This thesis demonstrates the value of ordinal logistic regression (OLR) for cross-sectional and longitudinal POS analysis, and proportion of net change as a simple, effective and widely replicable method for analysing POS scores change over time.

Four different kinds of analysis were employed in this thesis, of which each uses a different subset of the data, fulfils a different objective, and has its own advantages and disadvantages. Three of the four were completely novel applications of the POS. The discussion chapter shows how the four parts of the analysis support each other.

The priorities (following from the aim and objectives) were to retain separate outcome variables rather than combine them, to study the effect of time, and to conduct a replicable and rigorous analysis. Given seven outcomes, seven independent variables, four observations per person and 438 participants, the risk of spurious results was high, so a detailed plan was produced and followed. The more complex methods were only used when necessary. Simpler analysis has the benefits of ready interpretation, accessibility to clinicians in the field, and proximity to patient-reported experience. More sophisticated techniques remove data further from the patient. One reason for the use of extensions of logistic regression was that they produce odds ratios and a p-value, widely used for reporting and very familiar to the intended audience of these findings.

A six-point non-parametric ordinal outcome such as a POS score is too short for a linear variable and too long to model as categorical. Recoding the six-point scale into three or two increases the range of statistical techniques which can be brought to bear, including ordinal logistic regression. OLR is a very effective way to observe trends even though small changes may be lost, which was appropriate for the data. A trend for a variable to be associated with generally more severe outcome scores was more likely to be valid than, for example, the association of a variable with an outcome score of 3 as opposed to 0, 1, 2, 4 or 5. If I had retained a six-point scale I would have increased the risk of observing such trivial findings, which would obscure the larger trends. This thesis describes exploratory analysis in an uncharted area using a large number of equally important outcomes. This situation

is not uncommon in palliative care, which is multidimensional (thus requiring many outcomes) and which lacks an evidence base in many non-malignant conditions. This thesis presents a range of analytical techniques which may be applied to cross-sectional or cohort data on multidimensional problems in little-known populations.

Longitudinal research into HIV diagnosis is greatly lacking, as shown in the systematic review, and only the most basic before-and-after analysis has been conducted. The standard analysis protocol for univariate measurement of change in POS scores over time is to use paired t-tests between time points (Bausewein and Downing, in press). This method is recommended to clinicians for its simplicity but was not used here for three reasons. Firstly, the data are so far from parametric that it is not appropriate. Secondly, the t-test only indicates whether change is present, not the size of change. Thirdly, it was very likely that change would be present, so the null hypothesis of no change was not valid. Proportion of net change is a simple, effective technique to present the extent and direction of change over time at the population level, and the slowing rate of change(338). It can be conducted quickly and reliably using ordinary spreadsheet software or (for a small dataset) by hand, making it very suitable for use in resource-limited contexts, and it does not require repeated statistical tests or incur the risk of Type II error. To my knowledge this is the first use of proportion of net change in palliative care.

By contrast, the time-based (rather than month-based) longitudinal OLR requires expensive statistical software and the training to use it. Longitudinal analysis techniques with ordinal outcomes have been developed relatively recently. Longitudinal techniques are very valuable in palliative care and are particularly useful in a population defined by the time since an event, such as HIV diagnosis here. The methods used maximise efficiency and data usage. The longitudinal extension of logistic regression used 1511 of the 1524 observations collected (excluding 13 as outliers), thus producing more reliable and robust findings.

H Implications and conclusions

H.1 Is palliative care needed at diagnosis?

Multidimensional problems, of the type which in other contexts and populations are managed by palliative care, are prevalent and severe at HIV diagnosis. That in itself does not mean that palliative care is needed in this context and population. Need is defined as capacity to benefit and there are at least two situations in which a problem may be present without implying a corresponding need:

a) No intervention exists which could solve the problem
b) The problem is already solved

This study is the first to raise the possibility of palliative care at HIV diagnosis. No evidence has been published of the effectiveness of interventions at this time because it is not usual to report on newly-diagnosed people as a distinct group. A systematic review of palliative care in HIV showed positive results(140). It seems likely that interventions shown to work in populations with long-term HIV infection will also be effective in the post-diagnosis period, but there is a need for further research. Also, most palliative care interventions are complex and poorly understood, and evidence of effectiveness is lacking throughout the field, as shown by the limited number and quality of papers included in the systematic review.

As for the possibility that the problem is already solved, the data here show that all scores decrease over time. After three months, severe pain and symptoms are very scarce. It could be argued that current practice of non-palliative HIV care, other non-health interventions or simply the passage of time resolve palliative care-related problems at diagnosis. Some improvement is to be expected. Prior to diagnosis, participants probably had very little contact with health care services (otherwise they would have tested earlier). This study did not examine the role of current interventions, but they will have included common items such as non-opioid analgesics, antibiotics, topical cream for skin conditions etc. Some patients would have started TB treatment, which rapidly controls cough and night sweats and reduces fatigue. A regression to the mean effect may also be in effect. Participants took an HIV test on that day for a reason. Unmanageable symptoms or worries

probably played a role in the decision to test for at least some of the sample. Therefore the day of diagnosis would coincide with a spike in palliative care-related problems even among those who tested negative, because these problems would have prompted them to test.

However, the gradual population-averaged improvement observed under current care is not sufficient. Most people diagnosed with HIV do not remain in care. Patient retention is a major public health issue(421), especially in the period before ART eligibility assessment, and for those patients who are not eligible at diagnosis(143). Outside the ART programmes (where retention is managed much more carefully), most people with HIV do not return for regular clinic appointments(321). Patients lost to follow-up have much poorer outcomes with higher mortality and morbidity than those who remain in care(422)l(157). Health services have a limited opportunity in which to provide care before these patients are lost to follow-up. The high patient attrition suggests that either the barriers to care are insurmountable, or the perceived benefits do not outweigh costs. The barriers include the cost of transport(423) and service fees(238),

Lack of patient-centred care deters patients from remaining in health care. Qualitative interviews with patients in Uganda and Kenya found that they sought out facilities with a reputation for kind and respectful staff(346, 347). One of patients' main complaints against facilities was rudeness or contempt from staff. A relationship of trust was deeply important to patients, was highly praised when it was found and regretted when it was absent. Patient-centred care such as palliative care to build a rapport with patients from the first clinic visit could encourage and support retention. Management of symptoms which impede retention (such as fatigue, pain and vomiting) could also help patients to remain and to initiate ART at the appropriate time, without delays.

Retention was manipulated in this study be the use of transport reimbursement, so it cannot be studied as representative. In the literature, there is evidence that palliative care-related problems are barriers to retention in care. These include pain, hunger, hopelessness, and symptoms such as fatigue, confusion and nausea/vomiting(147). Current care may help to manage these problems, given time, but not if the problems themselves make care inaccessible.

In the first weeks after HIV diagnosis, patients are asked to take in a great deal of information and rapidly make decisions with long-term consequences. Practically they must return to the clinic at least once for a CD4 test result, which requires lost time from work, childcare, and money for transport. If put on the ART initiation pathway they will go through pre-ART counselling at which their readiness to undertake lifelong therapy is assessed. Patients are encouraged to disclose their status as soon as possible. Disclosure involves deciding to whom they can safely disclose their status, negotiating the conversation and dealing with the consequences which may include radical changes in family circumstances, violence or rejection. In more general terms [patients must plan how to adapt their daily life to deal with their HIV infection and treatment needs, and psychologically they need to accept the diagnosis as a reality.

The multidimensional burden identified in newly diagnosed patients is likely to impede their efforts to manage their diagnosis and plan for the future. Qualitative interviews in Zimbabwe found that newly diagnosed people had a good factual understanding of HIV but conceptualised it as social and physical death(258).They were unable to make good use of their knowledge and resources, instead employing avoidant coping strategies (denial and secrecy). Denial of HIV status is a cause of loss to follow-up, late ART initiation, and non-adherence, all of which are risk factors for mortality and morbidity. Not only for their immediate benefit, but also for long-term outcomes, multidimensional problems must be managed quickly, as their consequences may be severe.

In summary, there is evidence that

- Multidimensional problems are prevalent and severe at HIV diagnosis
- On average problems are reduced over time, for unknown reasons
- Many people do not remain in care long after diagnosis
- Multidimensional problems inhibit retention in care, disclosure, self-care and ART adherence
- In other populations with HIV, palliative care is effective at reducing multidimensional problems

Therefore I conclude that palliative care is needed at HIV diagnosis. It is an intervention of proven effectiveness in other contexts, it has low risks and its absence has serious and long-lasting negative effects. The consequences of this conclusion are discussed below.

H.2 Implications for policy and practice

As outlined in Sections B.2 and B.4, palliative care was originally envisioned as care for all with life-limiting conditions, but its policies and practice were developed in cancer. Wasson and George presented the ethical argument for expansion of palliative care to non-cancer conditions in 2001(424), basing it on justice (defined as fairness, equality and equity) and documented evidence of need. The HIV palliative care policies of the WHO(8, 129), UNAIDS and APCA(131), including their decision that palliative care begins at HIV diagnosis (quoted in Section B.3) have until now been based on justice but the evidence of need has been lacking.

Skilled, proactive multidimensional assessment is needed within two weeks of diagnosis, and preferably on the same day. Staff should aim to manage at least some problems on the day of diagnosis and thus give patients the motivation to return for further care. Care on the day of diagnosis will also help to prevent patients being lost to follow-up between diagnosis and first appointment, and returning home with the multidimensional burden reported here. Follow-up should continue for at least three months with repeated holistic assessment to identify new problems, particularly in psychosocial dimensions, and perhaps especially once physical pain and symptoms have been controlled. Recurrence and the appearance of new problems are to be expected. The WHO Pain Ladder(12) must be followed for pain management. Appointments should be as few as is commensurate with good care, to reduce the burden of travel time and costs on the patient. Multidimensional problems are not associated with CD4 count, therefore all patients must be assessed for palliative care needs at diagnosis, including those with a high CD4 count and WHO stage 1 or 2.

In sub-Saharan Africa, HIV palliative care is integrated with mainstream HIV services. The number of people with HIV, combined with the prevalence of

palliative care-related problems and the limited health resources, make integration the only feasible model of palliative care(217). Adequate palliative care will require training and support for clinical staff of all levels including doctors, nurses, medical officers and medical assistants. ‘Task shifting’, the transfer of health care tasks to staff with less training and fewer qualifications, has arisen in response to the HIV epidemic and shortage of health workforce(425). Palliative care training must be developed for all health care workers, of many disciplines, including those with minimal skills. Short palliative care training courses for generalist health staff in Africa already exist, and increasingly they are moving away from a focus on end of life care to incorporate the full trajectory of HIV disease. At the same time, quality must be maintained, and effective, efficient support systems must be developed to maximise the value of one palliative care specialist to a large number of generalist HIV staff.

Specialist palliative care must be available by referral for the minority of patients with multiple complex problems. Referral links must be strengthened with hospice teams for the management of intractable pain, severe psychological symptoms, and complex family needs. African hospices should develop small local centres or mobile services along the lines of Little Hospice Hoima and Mobile Hospice Mbarara, the services offered by Hospice Africa Uganda. Hospice staff should visit HIV outpatient centres to provide regular clinical support. It will never be possible to take African palliative care to scale through the traditional hospice model. The majority of care must be delivered by HIV HCWs, with palliative care specialists providing supervision, training and management of complex cases. Patients not in need of specialist palliative care should be referred back to an HIV health centre for continuing care.

Patients with limited function have a much higher multidimensional problem burden. For those who cannot make the journey to a health centre, home based care is necessary. These patients are likely to have pain and symptoms but are also at greater risk of psychological and spiritual problems which must not be overlooked while attending to more obvious problems. Community health workers should include generalist palliative care, using the Palliative Care Toolkit as a guide(130), but palliative care should not be exclusively community-based. It is not possible to train and equip community health workers to the point where they can

deliver palliative care without support, and there are not enough more highly trained HCWs to deliver home-based care as standard to everyone with HIV.

A multidimensional clinical assessment tool is needed which can be used regularly to monitor progress. Such a tool has been developed and is currently in use for a randomised controlled trial of palliative care alongside ART in Tanzania. It was based on around 20 instruments used in hospices and palliative care centres in Africa, and contributed in response to a call for examples. As a process outcome of the RCT, the tool will be assessed in terms of utility, acceptability and suitability, and it should be either improved or disseminated for wider use and development based on these findings.

Drug availability is another cornerstone of palliative care. Only two of the eleven facilities in this study stocked morphine. Lack of morphine has been framed as a denial of basic care and a violation of human rights(350). The delivery of morphine to all those who need it in Kenya and Uganda requires education of doctors, changes in prescription rules, and political will. These requirements are an element of the Public Health Model of palliative care(217). All steps of the Pain Ladder must be accessible to patients, including treatment of neuropathic pain.

The high prevalence and persistence of psychological, existential and spiritual problems over time indicate that training for spiritual care and counselling is a particularly important area. All the facilities in the study employed counsellors and nurse counsellors(346, 347), but in qualitative interviews it emerged that some counselling has become a form of didactic education rather than an opportunity for the patient to share concerns(426). Staff awareness of barriers to communication must be improved so that problems are recognised, especially to improve communication with patients who have little or no education

The study shows that symptoms are common at diagnosis but gives no information as to which symptoms they are. Until further evidence is available, clinical care should proceed on the assumption that the most common HIV symptoms are likely to occur at diagnosis. These are described in SectionB.1.iii; pain, fatigue, difficulty sleeping, weakness, weight change, skin problems etc. Treatment of these symptoms requires constant supplies of appropriate drugs. It is common for health

centres to experience drug stock-outs, sometimes caused by a limit to the amount they are permitted to order in one batch(363). The PHE included a pharmacy review and a paper is in progress detailing the findings from this and recommendations for improvement.

Palliative care in Africa also includes nutritional supplements or food, micro-finance programmes(231), legal advice, orphan care(234) and other forms of social support, which must be provided as needed. All these recommendations will require investment, but they are likely to be less expensive than the consequences of neglected problems at diagnosis. Prompt palliative care at diagnosis will be a worthwhile investment from the perspective of both the patient and the health care team, as good care could prevent future problems and support retention. A model using data from Cote d'Ivoire predicted the consequences of four interventions to reduce LTFU and found them all to be highly cost-effective due to their benefits to survival (422). The interventions used to prevent LTFU were (1) free ART at point of care; (2) free symptom management drugs; (3) resources to give HCWs in general health centres the skills of those in HIV-only centres; (4) a meal and transport costs refunds for patients attending scheduled appointments.

The number of people diagnosed with HIV per year in African countries is very difficult to establish. UNAIDS publishes annual reports detailing estimated prevalence and incidence by country, but diagnosis is not a commonly reported indicator. By contrast, high-income countries such as the UK and the USA monitor and publish exact numbers of positive HIV tests. Table H-1 displays diagnosis figures and estimates for Uganda, the UK, the USA and sub-Saharan Africa. In 2009, 6630 people were newly diagnosed with HIV in the UK, or 18 every day. Almost 43,000 people aged over 13 were diagnosed in the USA. Uganda does not publish such information. The number of infections in Uganda in 2009 is estimated at 135,000 according to UNAIDS and it is believed that 20% of people with HIV have been diagnosed(427). Making the very large assumption that the rate of testing keeps pace with the rate of infection, around 27,000 people are currently diagnosed with HIV every year in Uganda. (More diagnoses take place in the USA than Uganda despite the much lower prevalence, for two reasons; the population is larger, and a greater proportion of people with HIV learn their status.) The same figure of 20% is quoted for sub-Saharan Africa(29) where 1.8 million people are

believed to become infected every year(16), giving approximately 360,000 new diagnoses annually. At this scale, estimates are even less accurate. The range given in the table is extrapolated from the confidence interval around the published prevalence figure of 1.8 million, but it would probably be appropriate to add an additional error margin to the estimate of numbers diagnosed.

Table H-1: estimated number of newly diagnosed people per year by geographical region

Country	Number of people diagnosed per year	Data source	Year	Data reliability
Uganda	c.27,000	Based on 20% of infections(427)	-	Poor
UK	6630	Health Protection Agency, total report(428)	2009	Very good
USA	42,959 aged over 13	CDC	2009	Very good
Sub-Saharan Africa	360,000 (320,000-400,000)	UNAIDS 2010 Report(16) and Universal Access Progress Report(29)	2009	Poor

Universal access to ART requires a scale-up of testing services to match the incidence of infection(29), since a test is the gateway to ART. The number of newly diagnosed people per year should therefore increase, especially in low-income countries where the majority of people live who lack access to ART. This increase may be difficult to detect, as current data on the number of new diagnoses per year are so poor. Ministries of health should attempt to report better estimates of the number of people diagnosed per year in their countries. This information is needed to plan services and predict needs. It is a paradox that figures on incidence and prevalence of HIV are estimated from real data on the number of people diagnosed (or tested anonymously), yet the estimates are widely available whereas the raw data are hard to obtain. This is an indication that diagnosis is not viewed as important in public health terms.

H.3 Implications for research

Evidence of problems is not meaningful unless interventions to solve those problems are developed and tested. Further evidence is needed of the effectiveness of integrated palliative care on patient-centred outcomes, in HIV generally and at diagnosis in particular. In some cases, particular interventions must be tested, but it is especially important to prove the effectiveness of the patient-centred individual assessment which typifies palliative care. As described above, integrated care is the only viable model. Randomised controlled trials of palliative care alongside ART are underway in South Africa and Kenya, but like many studies they exclude the newly diagnosed (one month since ART initiation is required). Interventions developed for general HIV populations or for other diseases and conditions should be tested at diagnosis in randomised controlled trials.

Any estimate of palliative care problems based solely on physical symptoms and pain is likely to grossly underestimate the level of need. Social and spiritual problems are more prevalent and severe than physical and psychological symptoms in this sample, but these areas are not well understood. Need to share feelings and lack of help/advice are the areas of greatest need and least certainty. Research should concentrate on these areas which have been shown to be of great importance to patients. Similar research is needed in other countries and contexts, given the differences found between Uganda and Kenya. This study proves that data collection on the day of HIV diagnosis is possible, with very low refusal rates.

The POS indicates the areas in which problems occur. More research must identify in more detail the nature of symptoms and concerns, to inform the development of care protocols. Complementing this, qualitative interviews should be conducted with newly diagnosed participants to form a more accurate assessment of the problems which are most important to patients and to understand their origins and barriers to care. Interviews at such a vulnerable time must be undertaken sensitively. Experience of interviews in bereavement should be used for reference.

In palliative care, the unique experience of the individual is central. This thesis has presented averages and overall associations. Further work with this dataset should explore the individual-level trajectories of change over time, possibly using visual graphical analysis. Qualitative research will also be invaluable to understand the diversity of individual experience and needs. The meaning to patients of the seven outcomes measured here should be investigated further using qualitative interviews. In particular, need for help and advice is the least understood and the most severe problem.

Future development of the POS should involve reconsideration of the question on help and advice for the family. Over half the sample reported the worst possible score at baseline, which would often suggest a ceiling effect, but in this case the option is ‘received no help and advice at all’, the natural limit of the question. To identify those in greatest need it may be necessary to split this question into two or more, such as distinguishing between practical matters and information needs. As discussed above in the implications for policy and practice, the findings that palliative care-related problems are common at HIV diagnosis and are not related to disease stage will require palliative care services to expand to reach more people with chronic, rather than terminal, illness. Audit, clinical and research assessment tools such as the POS must be continuously monitored to ensure they are appropriate for the population in which they are used. As the POS is increasingly applied in populations with early-stage HIV for whom practical matters, information and decision-making are of great importance, the seventh POS question should be examined to ensure it accurately reports patient-centred problems in these areas.

H.4 Conclusion

The aim of this thesis was to determine the palliative care-related problems experienced by people in Kenya and Uganda in the two weeks following diagnosis of HIV, and how those problems change over the subsequent three months. Palliative care is

> *"an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual"* (11).

The findings show that people newly diagnosed with HIV are indeed "*facing the problems associated with life-threatening illness*". The problems that typically occur at the end of life are also highly prevalent and severe at HIV diagnosis, such as lack of help and advice(65% severe problems), difficulty sharing feelings(53%), loss of peace(19%), worry(11%), feeling that life is not worthwhile(10%), pain(6%) and symptoms(3%), and for many patients they persist over time. Social and relational problems are especially common at diagnosis, leaving patients unable to communicate their concerns or receive the support they need. Psychological and physical problems are widespread and may impede access to care. Patients whose physical function is limited seem to have fewer difficulties receiving help/advice(OR=0.6) and sharing their feelings(OR=0.5) but have a much higher burden of physical(OR=3.2), psychological(OR=1.6) and spiritual(OR=1.7) problems.

On average, over time, the burden of problems goes down in all areas, but considerable variation is hidden within this average and many patients experience worsening problems or a recurrence. Patients who do not find their lives worthwhile experience little improvement, and spiritual problems are more prevalent after three months than two. After initiation of ART, patients report lowered symptom burden (OR=0.7), fewer problems getting help and advice (OR=0.7), and more peace (OR=0.6), but the effects are weak. ART recipients continue to experience palliative care-related problems, especially in psychological domains.

Little is known about the care patients receive during this time and the effect of any interventions on outcomes, but the group is representative of patients at large health centres in receipt of PEPFAR funding to provide multidimensional care and support, so the care is expected to be better than average for an HIV outpatient in Africa. Cross-sectional findings are supported in the sparse HIV diagnosis literature, while the longitudinal results are some of the first ever presented.

The findings provide the first evidence in support of the policies of the WHO, UNAIDS and APCA regarding palliative care at diagnosis in Africa. This thesis presents the most extensive and highest quality evidence yet discovered for multidimensional problems at diagnosis. In particular, it is the first study to draw a representative sample of newly diagnosed outpatients in Africa, who comprise the majority of people diagnosed with HIV, and the first in the world to measure multidimensional patient-centred problems at that time. Generalisability to other contexts is limited because the two countries in the study had quite different results, but until further research is produced, the findings should be used to inform decision making in other contexts, as the best available example.

This thesis has also presented methodological contributions to the literature in the form of a model for exploratory analysis of multidimensional outcomes cross-sectionally and over time. It has pioneered the use of ordinal and longitudinal extensions of logistic regression for analysis of short non-parametric ordinal scales and introduced proportion of net change as a statistical technique for non-specialists.

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Appendix A: data collection instruments

The APCA African POS & ECOG

Question number	ASK THE PATIENT Questions 1-7	POSSIBLE RESPONSES	ANSWER
Q1	Please rate your pain (from 0 = no pain to 5 = worst/overwhelming pain) during the last 3 days	**0 = No pain at all** **1 = Slight pain** **2 = Moderate pain** **3 = Severe pain (interferes with activities of daily life)** **4 = Very severe pain** **5 = Overwhelming. The worst pain you can imagine**	
Q2	Have any other symptoms (e.g. nausea, coughing or constipation) been affecting how you feel in the last 3 days?	**0 = no, not at all** **1 = slightly** **2 = moderately** **3 = severely** **4 = very severely** **5 = overwhelmingly**	
Q3	Have you been feeling worried about your illness in the past 3 days?	**0 = Not at all worried** **1 = Worried very occasionally** **2 = Worried some of the time** **3 = Worried a lot of the time** **4 = Worried most of the time** **5 = Worried all of the time**	
Q4	Over the past 3 days, have you been able to share how you are feeling with your family or friends?	**0 = Not at all** **1 = Only once** **2 = Occasionally** **3 = Fairly frequently** **4 = Often** **5 = Yes, I've talked freely**	
Q5	Over the past 3 days have you felt that life was worthwhile?	**0 = Not at all** **1 = Not very often** **2 = Occasionally** **3 = Some of the time** **4 = Most of the time** **5 = Yes, all the time**	
Q6	Over the past 3 days, have you felt at peace?	**0 = Not at all** **1 = Not very often** **2 = Occasionally** **3 = Some of the time** **4 = Most of the time** **5 = Yes, all the time**	
Q7	Have you had enough help and advice for your family to plan for the future?	**0 = None** **1 = Very little** **2 = For a few things** **3 = For several things** **4 = For most things** **5 = As much as wanted**	
	Thank the patient		

	ASK THE CARER Questions 8, 9 and 10 ONLY if consent given by patient and carer		
Q8	How much information have you and your family been given?	**0 = None** **1 = Very little** **2 = Some** **3 = Quite a lot** **4 = A great deal** **5 = As much as wanted** **7 = N/A, no carer/consent not given** **8 = carer not present at time of interview**	
Q9	How confident does the family feel caring for ____?	**0 = Not at all** **1 = Not confident about many things** **2 = Confident about a few things** **3 = Confident about some things** **4 = Confident about most things** **5 = Very confident** **7 = N/A, no carer/consent not given** **8 = carer not present at time of interview**	
Q10	Has the family been feeling worried about the patient over the last 3 days?	**0 = Not at all worried** **1 = Worried very occasionally** **2 = Worried some of time** **3 = Worried a lot of the time** **4 = Worried most of the time** **5 = Worried all of the time** **7 = N/A, no carer/consent not given** **8 = carer not present at time of interview**	
	ECOG (rated by the interviewer)		
Q11	Physical function of patient	**0= fully active, able to carry on all pre-disease performance without restriction** **1=Restricted in physically strenuous activity but ambulatory and able to carry out light work, e.g., light house work, office work** **2=Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours** **3=Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours** **4=Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair**	

Demography

Demography questionnaire

P1	Please indicate the patient's gender		**male=1, female=2**	☐
	I would like to ask you a few questions about your background:			
P2	How old are you (years)?			☐☐
P3	What is the highest level of education you attended?		**none=1** **attended primary=2** **attended secondary=3** **diploma=4** **degree or higher=5**	☐
P4	What is the main material used to make the floors of your house?	natural finished	**earth, mud, sand=1** **cement=2** **linoleum=3** **parquet/polished wood=4** **tile=5** **carpet=6** **stone=7**	☐
P5	What is the main material used to make the walls of your house?	natural rudimentary finished	**thatched/straw=1** **mud and poles=2** **un-burnt bricks=3** **burnt bricks with mud=4** **cement blocks=5** **stone=6** **Wood timber=7** **burnt bricks with cement=8**	☐
P6	What is the main material used to make the roof of your house?	natural finished	**thatched=1** **wood/planks=2** **corrugated iron sheets=3** **asbestos=4** **tiles=5** **tin=6** **cement/concrete=7**	☐
P7	What type of toilet do you use at home?		**private flush=1** **private VIP latrine =2** **private traditional pit (covered)=3** **private traditional pit (uncovered)=4** **public/shared=5** **bush/field/other=6**	☐
P8	How far from the facility do you live? (kilometres) If not known, ask for means of travel and time taken to estimate distance.		**don't know=888**	☐☐☐ km

P9	What is the main source of drinking water for your house?	safe	**bottled=0**	☐
			piped inside house=1	
			piped outside house (yard, public tap)=2	
			protected well=3	
			borehole=4	
			spring/rain water=5	
		unsafe	**unprotected well=6**	
			river/stream/pond=7	
			tanker truck=8	
P10	What type of fuel does your household mainly use for cooking?		**electricity=01, lpg/natural gas=02**	☐☐
			biogas=03, paraffin/kerosene=04	
			coal=05, charcoal from wood=06	
			firewood=07, straw/shrubs/grass=08	
			dung=10, no food cooked in household=11	
P11.1	Does anyone in the household own a …?	car	**yes = 1, no = 2**	☐
P11.2		bicycle		☐
P11.3		refrigerator		☐
P11.4		television		☐
P11.5		mobile phone		☐
P11.6		radio		☐

Now I would like to ask you a few questions about your HIV diagnosis:

P12	What date did you enrol into this facility?	**dd/mm/yy**	☐☐☐☐☐☐
		unknown day= 15, unknown month= 06, unknown year =888888	
P13	why did you visit this facility today?	**new illness/well-being issue = 1**	☐ Place from which referred (2), or other reason for attending (5): _____
		referred = 2 (from where)	
		obtain medication = 3	
		HIV test result = 4	
		other = 5 (specify)	
P14	date diagnosed HIV+	**dd/mm/yy**	☐☐☐☐☐☐
		unknown day= 15, unknown month= 06, unknown year =888888	
P15	date started on ARV treatment	**dd/mm/yy**	☐☐☐☐☐☐
		unknown day= 15, unknown month= 06, unknown year =888888	
		777777=not on ARV	
P16	Current WHO clinical stage (1-4)	**8=don't know**	☐☐
P17	Most recent CD4 count	**don't know=8888**	☐☐☐☐☐☐
P18	date of most recent CD4 count	**dd/mm/yy**	☐☐☐☐☐☐
		unknown day= 15, unknown month= 06, unknown year =888888	
P19	How many dependants do you have? (family members who are dependent on you including children)		☐☐

Appendix B: ethical approvals

KENYA MEDICAL RESEARCH INSTITUTE

P.O. Box 54840-00200 NAIROBI, Kenya
Tel: +254 (020) 2722541, 2713349, 0722-205901, 0733-400003, Fax +254 (020) 2720030,
E-mail: director@kemri.org; info@kemri.org Website: www.kemri.org

KEMRI/RES/7/3/1

23 March 2007

The Principal Investigators

Dear Sirs,

RE: PEPFAR Public Health Evaluation Protocol

I have perused the above protocols and while I have granted provisional approval for the conduct of the proposed survey I wish to point out the following:-

(a) Strictly speaking these surveys in my opinion constitute research and ought to be treated as such. Accordingly they should and will in future be subjected to review of both science and ethics as the case may require in the normal manner.

(b) Reports/Results of the survey should be communicated to the ERC.

(c) There is need for participation of local investigators as a matter of policy.

(d) The ethical principle of beneficence must always be borne in mind and reflected in the protocols.

Yours faithfully,

A. D. O. RACHIER
CHAIRMAN
KEMRI/NATIONAL ETHICAL REVIEW COMMITTEE

KENYA MEDICAL RESEARCH INSTITUTE

P.O. Box 54840 - 00200 NAIROBI, Kenya,
Tel: (254) (020) 2722541, 2713349; 0722-205901, 0733-400003; Fax (254) (020) 2720030,
E-mail: kemri-hq@nairobi.mimcom.net; director@kemri.org Website: www.kemri.org

Research/Non-research /Human Subjects Determination.

[Request to Classify A Proposal/Project as Not Involving Human Subjects or Non-Research -NRD]

This form should be used to submit to ***The Director KEMRI*** *proposals for activities or investigations that do not require Ethical Review Clearance because they do not involve identifiable Human Subjects or they are eligible to be classified as Non-research – **NRD]***

ProjectTitle PEPFAR Public Health Evaluation: Palliative Care

Project Location(s)/Sites: 60 PEPFAR-funded palliative care sites, randomly selected, listed in the protocol

Project Officer(s): PI's Dr Richard Harding
Prof Irene Higginson

Institute Affiliation(s): King's College London

Contact Telephones: ++44 (0)20 7848 5589
++44 (0)20 7848 5516

E-mail Addresses: richard.harding@kcl.ac.uk
irene.higginson@kcl.ac.uk

Proposed Project Dates: Start 1/Apr/2007 Ending: 1/Apr/2009

Categories of data collection that do not constitute Research or human subjects research include the following: Please check appropriate category for this project:

1. Activity is not research: The primary intent is a public health practice for disease control activities:

___**A. Epidemic/endemic disease control** activity: data collected relate directly to disease control needs.

___**B. Routine disease surveillance** activity: data used for disease control or policy purposes.

_X_**C. Program evaluation** activity: data used primarily for that purpose.

___**D. Post-marketing surveillance:** data to monitor efficacy and/or adverse effects of a new regimen, drug, vaccine or device.

-OR-

II. <u>Activity is research BUT does not involve identifiable human subjects:</u>

___**A. Activity is research involving collection/analysis of data** about health facilities or other organizations or units which are not individual persons.

OR

___**B. Activity is research involving data and /or specimens from deceased persons.**

OR

___**C. Activity is research using unlinked anonymous data or specimens:**

_____1. Identifying information either was not obtained **<u>or</u>** has been removed so that data cannot be linked or re-linked with identifiable human subjects.
(Note: under certain conditions, research *may* qualify as non-human subjects when identifiers are removed by local staff)

_____ 2. Data or specimens were collected for another purpose but are now available anonymously.

Please attach the project protocol description in the standard form to clarify/ justify the Non human subjects / Non research nature of this proposal.

☐ *Check here if this request is an* ***amendment*** *of an existing non-research determination [**NRD**].*

.....
.....

Approved by: _____ **Date** 26 / 03 / 07

Dr. Davy K Koech:
Director KEMRI

Additional Comments:

1. Although this project qualifies under NRD, investigators/project officers are expected to adhere to **ETHICAL** principles and standards by respecting and protecting to the extent possible the privacy, confidentiality and autonomy of participants. All applicable National Privacy Laws must be followed.
2. Informed Consent where applicable must be obtained appropriately.

Uganda National Council For Science and Technology

(Established by Act of Parliament of the Republic of Uganda)

Your Ref: .....

Our Ref: .....SS 1964.....

Date: ....07/05/07..

Dr. Richard Harding
African Palliative Care Association
P.O Box 72518
Kampala

Dear Dr. Harding,

RE: RESEARCH PROJECT, "PEPFAR PUBLIC HEALTH EVALUATION: PALLIATIVE CARE" DATED MARCH 2007

This is to inform you that the Uganda National Council for Science and Technology (UNCST) approved the above research proposal on **April 30, 2007**. The approval will expire on **April 30, 2008.** If it is necessary to continue with the research beyond the expiry date, a request for continuation should be made in writing to the Executive Secretary, UNCST.

Any problems of a serious nature related to the execution of your research project should be brought to the attention of the UNCST, and any changes to the research protocol should not be implemented without UNCST's approval except when necessary to eliminate apparent immediate hazards to the research participant(s).

This letter also serves as proof of UNCST approval and as a reminder for you to submit to UNCST timely progress reports and a final report on completion of the research project.

The Resident District Commissioner(s) of Apac, Bugiri, Bundibugyo, Bushenyi, Busia, Jinja, Kabarole, Kaberamaido, Kampala, Kayunga, Kisoro, Kitgum, Kumi, Kyenjojo, Lira, Mbarara, Mukono, Nakapiripirit, Pallisa, Rakai, Rukungiri, Soroti, Tororo, Wakiso district(s) in which the study will be conducted is informed by copy of this letter, and is kindly requested to give you the necessary assistance to accomplish the study.

Yours sincerely,

Jane Nabbuto
for: Executive Secretary
UGANDA NATIONAL COUNCIL FOR SCIENCE AND TECHNOLOGY

LOCATION/CORRESPONDENCE
Plot 3/5/7 Nasser Road
P.O.Box 6884
KAMPALA, UGANDA

COMMUNICATION
TEL: (256) 41-250499, (256) 41- 705500
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E-MAIL: uncst@starcom.co.ug
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File No. SS 1964

Name. RICHARD HARDING

Address. AFRICAN PALLIATIVE CARE P. O BOX 72518 KAMPALA

Nationality BRITISH

Title of Research Project

PEPFAR PUBLIC HEALTH EVALUATION: PALLIATIVE CARE

Date of Issue 07/05/07

Valid Until 30/04/08

ANY ONE FINDING THIS CARD SHOULD HAND IT IN AT THE NEAREST POLICE STATION

No. 0907/1

Holder's Signature.....

UGANDA NATIONAL COUNCIL FOR SCIENCE & TECHNOLOGY P O BOX 6884 KAMPALA - UGANDA

Certified Photograph

Executive Secretary
Uganda National Council for
Science and Technology
P.O. Box 6884,Kampala

THIS CARD IS A PROPERTY OF THE UGANDA GOVERNMENT

Renewed until .....

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Executive Secretary

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Executive Secretary

Renewed until .....

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Executive Secretary

Renewed until .....

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Executive Secretary

Uganda National Council For Science and Technology

(Established by Act of Parliament of the Republic of Uganda)

Your Ref:.....

Our Ref:.....SS 1964

Date:.....16/04/08.....

Dr. Richard Harding
African Palliative Care Association
P.O Box 72518
Kampala

Dear Dr. Harding,

The Uganda National Council for Science and Technology (UNCST) has granted your request for approval to continue with the study entitled, **"PEPFAR Public Health Evaluation: Palliative Care".** The approval will expire on April 30, 2009. If, however, it is necessary to continue with the research beyond this expiry date, a request for continuation should be made to the Executive Secretary, UNCST.

The Resident District Commissioners of Apac, Bugiri, Bundibugyo, Bushenyi, Busia, Jinja, Kabarole, Kaberamaido, Kampala, Kayunga, Kisoro, Kitgum, Kumi, Kyenjojo, Lira, Mbarara, Mukono, Nakapiripirit, Pallisa, Rakai, Rukungiri, Soroti, Tororo and Wakiso Districts in which the study will be conducted are informed by copy of this letter, and are kindly requested to give you the necessary assistance to accomplish the study.

Yours sincerely,

Leah Nawegulo
for: Executive Secretary
UGANDA NATIONAL COUNCIL FOR SCIENCE AND TECHNOLOGY

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Dr Richard Harding
Department of Palliative Care, Policy and Rehabilitation
King's College London
Weston Education Centre
Cutcombe Road
London SE5 9RJ

Friday 11th January 2008

Dear Dr Harding

CREC/06/07-140 PEPFAR Public Health Evaluation Palliative Care

Thank you for the requested modifications sent by Vicky Simms. I am pleased to inform you that the changes to the Information Sheets have been approved.

We wish you every success with this work.

Yours sincerely

Rowena Lamb
Research Ethics Officer

Patient information sheet and consent form

Patient Information Sheet - PEPFAR Evaluation of Care

We would like to invite you to participate in a service evaluation. Before you decide about taking part, it is important for you to understand why the evaluation is being done and what it will involve. Please listen to the following information and ask if anything is unclear.

We are looking at how people attending this facility are cared for, and if it might be made better. We are asking every new patient, or patient who has a new problem, to take part. You and about 100 other patients have been approached in this facility.

You do not have to take part. If you do, you can withdraw from an interview at any time, or in between interviews, and you don't have to give a reason. Taking part, withdrawing, or not taking part will not affect the care you receive at all. If you take part you will be given this sheet to keep and sign a consent form to show that you have agreed to participate.

I will interview you at your usual place of care at a time as close as possible before your appointment. You will not have to see anyone not involved in your care. I will ask you questions about you and your health, e.g. how you have been feeling, have you had any pain. The questions will take no more than 30 minutes to answer. I would also like to ask a family member who cares for you a few questions about their well-being, if applicable and only if you allow us to. You can participate in the evaluation even if you do not want me to talk to your family. I will ask you a set of questions every month for 3 months. After that there will be no more things for you to do for this evaluation.

The information I write down during the interview will be confidential. Your personal details (e.g. name and address) will not be given to anyone and your answers will be kept separately. We will use all responses to write up reports on how we think patients should be cared for. Nothing you say will be identified as coming from you. You may withdraw your responses at any time until they are used in the final report.

This evaluation is organised by King's College London (UK), an African Care association (APCA) and this care facility. It is funded by PEPFAR, part of the US government. The Ugandan/Kenyan and KCL (ref CREC/06/07-140) Ethics Committees have reviewed and approved this study for your protection.

If you'd like to talk to someone about the evaluation please contact APCA **Uganda/Kenya <delete as applicable>**

<insert relevant name, address and telephone number>

Facility Name:…….. September 2007
Facility ID:……

PEPFAR Evaluation of Care - Consent Form

Participant's Statement:

- I confirm that I have read and understand the information sheet dated September 2007 for the above study and have had the opportunity to ask questions.

- I understand that if I decide at any other time during the evaluation that I no longer wish to participate in this project, I can notify the researchers involved and be withdrawn from it immediately without my medical care or legal rights being affected.

- I consent to the processing of my personal and medical information for the purposes of this evaluation. I understand that such information will be treated as strictly confidential.

- I agree to my responses being stored anonymously at APCA and KCL for 7 years.

- I agree to take part in the above study.

- I do/do not/not applicable **(circle as applicable)** agree to the health worker asking the member of my family accompanying me today some questions about their well-being.

_____(name)

Signed or fingerprint:…… **Date**……

Health worker's Statement:

I_____(name)

confirm that I have carefully explained the nature and demands of the proposed research to the volunteer.

Signed:…… **Date**……..

Appendix C: description of clinical facilities

Table 0-1: number of patients per facility in 2007

ID	Facility	Number of patients in 2007	Number of new patients in 2007
K1	Sindo Sub District Hospital	missing	246
K2	Nyeri Provincial General Hospital	3031	377
K3	Thika District Hospital	4334	463
K4	Bomu, Mombasa	1126	796
K5	Kericho District Hospital	4963	547
K6	Chulaimbo	5975	422
U1	TASO Rukungiri	4772	401
U2	AIDS Information Centre (AIC) Kampala	missing	missing
U3	Mulago Infectious Disease Institute (IDI)	9698	828
U4	Joint Clinical Research Centre (JCRC) Kampala	7062	5774
U5	Mbarara	5602	683

The table above shows the total number of patients, and number of new patients, registered at each of the eleven facilities in 2007 according to PEPFAR figures. The information was not available for AIC Kampala, which provides counselling and testing services to a large number of people who are not defined as patients according to PEPFAR criteria. Further information on each facility is given below.

Kenya

Bomu – Bomu Medical Centre is an NGO based in Mombasa and a USAID Centre for Excellence in HIV/AIDS care. It has numerous links with international charities and organisations including CDC, the Stephen Lewis Foundation and Family Health International. In the model of Kenyan public hospitals, Bomu has a CCC (Comprehensive Care Centre) providing all its HIV services, in line with the usual model of HIV care in Kenya.

Chulaimbo – Chulaimbo Subdistrict Hospital is on the outskirts of Kisumu in western Kenya. Following a contested presidential election in December 2007, civil unrest caused severe problems for two months, with Kisumu one of the worst affected areas.

Kericho –The Kenya Medical Research Institute/Walter Reed Project Clinical Research Center is a United States Military HIV Research Program field centre. Its primary objective is to develop an HIV vaccine. Several long-term cohort studies are operating from Kericho.

Nyeri – Nyeri Provincial General Hospital is the referral hospital for Central Province. The study was based at Nyeri CCC, situated in the grounds of the hospital.

Sindo - Sindo District Hospital in Nyanza, in western Kenya was also affected by civil unrest following the election. Violence was targeted at particular ethnic groups. Staff adopted a policy of giving patients two months' supply of drugs instead of one, to save them a visit. Although Sindo Hospital is a public hospital, the CCC is operated by an NGO specialising in family-centred HIV care.

Thika – about two hours' drive from Nairobi, Thika District Hospital has recently built a new CCC with funding from donations. Like Chulaimbo, Nyeri and Sindo, it is a government-run public hospital.

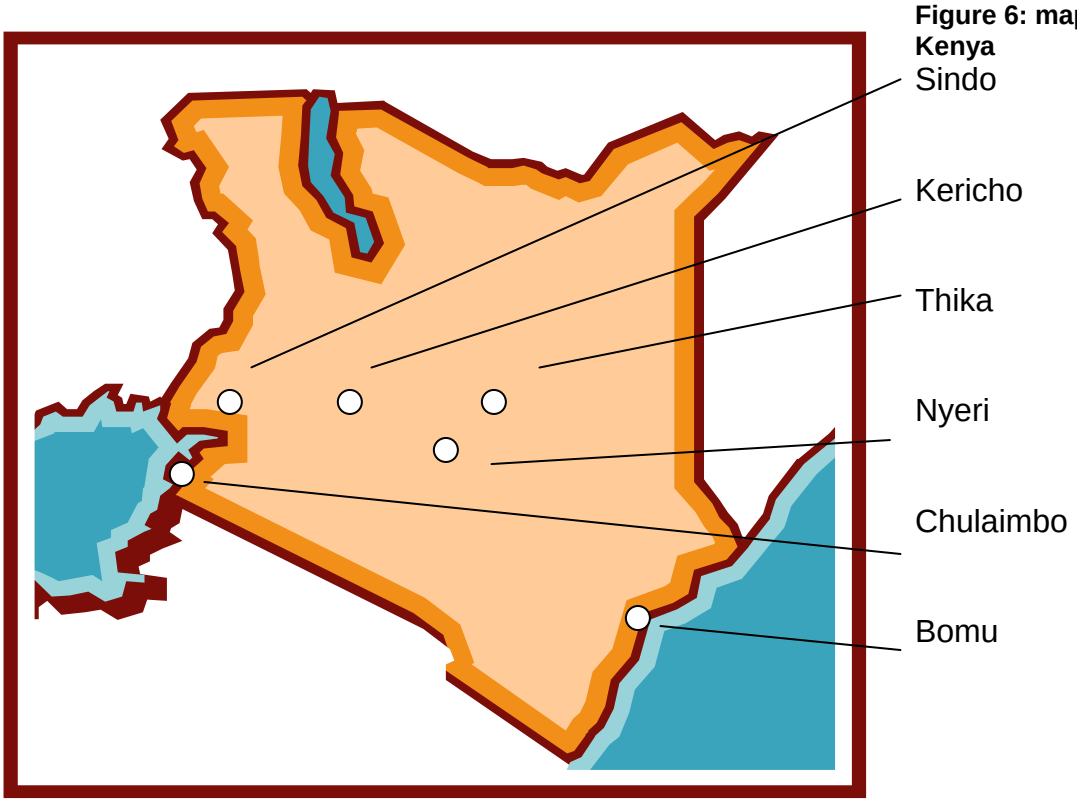


Figure 6: map of Kenya

Uganda

AIC – the AIDS Information Centre in Kampala opened in 1990, with the aim of preventing HIV infection by encouraging testing. It now has eight branches around the country and is the leading provider of counselling and testing services in Uganda. It recently began to provide ART.

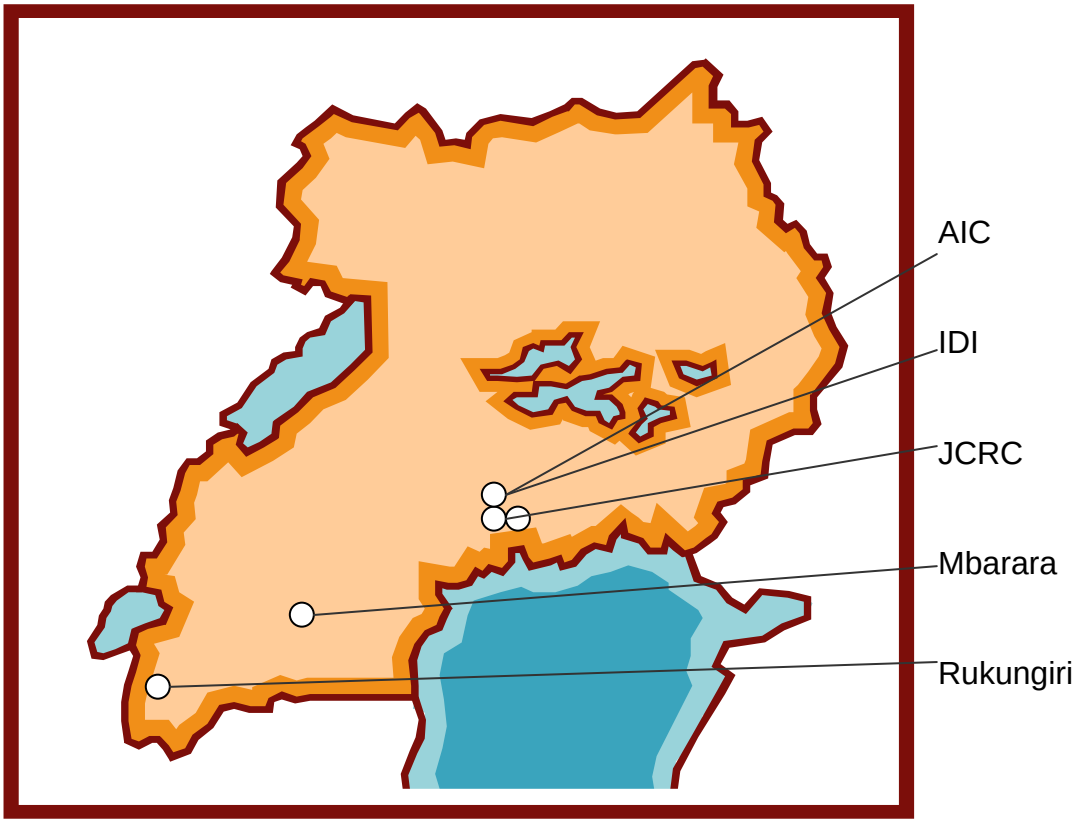
IDI - The Mulago Hospital infectious Disease Institute. Mulago Hospital in Kampala is one of Uganda's two teaching hospitals. IDI was established in 2004 as a centre for both clinical care and research, supported by the Academic Alliance for AIDS Care and Prevention in Africa and several other partners including Pfizer. Although it is based in a public hospital, IDI is run as an NGO and provides free services.

JCRC – The Joint Clinical Research Centre is a collaboration between the Ministries of Health and Defence and Makerere University School of Medicine. It has provided ART to over 30,000 clients since 1996, making it possibly the largest ART provider in sub-Saharan Africa (JCRC website). JCRC has collaborations with a number of universities and undertakes many research projects every year.

Mbarara – Mbarara Regional Referral Hospital is a public hospital in western Uganda, around 180 miles from Kampala. All patients with HIV are referred to the ISS (Immune Suppression Syndrome) clinic, where the study was based. Mbarara is the most government-centred of the Uganda facilities.

TASO Rukungiri – The AIDS Support Organisation is a model for grassroots HIV care, support and activism in developing countries. Founded in 1987 by a small group of people with HIV, it has provided care and support to over 200 000 people. The programme began providing ART in 2004 and has scaled up provision to 20 000 clients. TASO Rukungiri, one of eleven service centres, is located in southwest Uganda.

Figure 7: map of Uganda



Appendix D: loadings onto wealth index factor in principal components analysis

Table 0-1: loadings onto wealth factor

variable	**loading**
Earth floor	-0.314
Unsafe water	-0.195
Own a television	0.143
Private flush toilet	0.133
Own a refrigerator	0.122
Mud and poles/unburnt brick/brick with mud walls	-0.122
Own a mobile phone	0.111
Protected well/borehole/rain water	-0.101
Own a car	0.081
Natural roof	-0.068
Piped water inside house	0.046
Electricity/natural gas/LPG for cooking fuel	0.034
Public/shared/bush latrine	0.024
Own a radio	0.024
Corrugated iron roof	-0.021
Own a bicycle minus	-0.014
Tiled/cement/asbestos/tin roof	0.011
Polished wood/tile/carpet floor	-0.009
Paraffin/kerosene/coal cooking fuel	0.006
Piped water outside house	<0.001
Charcoal for cooking fuel	<0.001
Latrine	<0.001
Cement floor	<0.001

Appendix E: Publications

Simms V., Higginson I.J., Harding R. (2011). What palliative care-related problems do patients experience at HIV diagnosis? A systematic review of the literature. Journal of Pain and Symptom Management. Epublished before print

Review Article

What Palliative Care-Related Problems Do Patients Experience at HIV Diagnosis? A Systematic Review of the Evidence

Victoria M. Simms, MSc, Irene J. Higginson, PhD, and Richard Harding, PhD
King's College London, Cicely Saunders Institute, London, United Kingdom

Abstract

Context. Palliative care is an essential element of HIV care throughout the disease trajectory, but there is a lack of information to guide clinical care at HIV diagnosis.

Objectives. This systematic review aimed to identify and appraise the evidence of palliative care-related problems at HIV diagnosis.

Methods. The search strategy combined the term "HIV" with seven key words derived from the World Health Organization definition of multidimensional palliative care, in a systematic search of four databases. Abstracts and papers were screened to identify those recording problems within six months of HIV diagnosis in adults. Sample descriptions, aims, methods, and prevalence findings were extracted from these papers into common tables.

Results. Of 5443 titles retrieved, 65 met the inclusion criteria and 34 were retained. Papers included 27 original studies and seven secondary analyses of patient's records, with great heterogeneity in design, sample definition, and outcome measures. Physical and psychological symptoms were highly prevalent (pain 11%–76%, weight loss 8%–89%, fever 32%–89%, diarrhea 6%–54%, anxiety 36%–95%, and depression 18%–47%). At HIV diagnosis, well-being was impaired, suicidal thoughts were frequent, and peace and calmness were reduced. Participants lacked emotional support and feared the reaction of their families. Practical problems included hunger, homelessness, reduced ability to work, and need for childcare. Studies had methodological failings such as the use of unvalidated tools and lack of clarity reporting results.

Conclusion. People who have recently been diagnosed with HIV have multidimensional palliative care-related problems. HIV care and support services need to assess and manage problems using integrated palliative care, with referral for complex problems. Patient centeredness must be a principle of HIV clinical research. J Pain Symptom Manage 2011;42:734–753.

Key Words
HIV, multidimensional, newly diagnosed, palliative, systematic review

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0885-3924/$ - see front matter
doi:10.1016/j.jpainsymman.2011.02.014

Introduction

Palliative care requires the early identification; thorough assessment; and effective treatment of all problems, physical, psychological, spiritual, and social, in life-limiting illness.[1] There is evidence that palliative care for HIV is effective in the domains of pain and symptom control, anxiety, insight, and spiritual well-being,[2] although the literature is limited; most studies predate the availability of antiretroviral therapy (ART), almost all are of patients with advanced disease, and very few have been conducted in sub-Saharan Africa where two-thirds of people with HIV live.[3]

World Health Organization (WHO) policy states that "palliative care should be incorporated as appropriate at every stage of HIV disease, and not only when the patient is dying,"[1] and that palliative care should be used alongside ART as needed, not as a substitute. Similarly, the Joint United Nations Program on HIV/AIDS (UNAIDS) guidelines confirm that all people living with HIV should be provided with effective palliative care,[4] and the WHO advocates the integration of palliative care into comprehensive care and support for people living with HIV from diagnosis to the end of the life.[5] To fulfill this requirement, it is necessary to understand what constitutes appropriate palliative care intervention at the different stages of HIV disease. There is evidence that people with HIV have palliative care-related problems in both early[6] and advanced disease,[7] which persist with the use of ART.[8] However, the delivery of care to meet these policies is challenged by a lack of detailed information about palliative care-related problems at the time of HIV diagnosis.

The majority of the HIV palliative care literature relates to the end of life, reflecting the discipline's origins in terminal care. Modern palliative care encompasses the whole trajectory of life-limiting illness from diagnosis to death. However, more recent studies of palliative care in earlier stages of HIV disease may not make reference to the time since diagnosis. Knowledge of the multidimensional problems that patients experience at HIV diagnosis is required to plan services, inform patient and family assessment, educate staff, and guide clinical care. The aim of this study was to systematically review the literature to identify and appraise the evidence of multidimensional palliative care-related problems at HIV diagnosis. A secondary aim was to identify gaps in the literature.

Methods

Review Question

The review question was "What palliative care-related problems do adults experience at the time of HIV diagnosis?"

Search Strategy

The review was carried out following Centre for Reviews and Dissemination procedures and using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist.[9]

Databases and Date of Search

OVID Medline, PsycINFO, Embase, and PubMed were searched from 1981 to September 2009 (the search date).

Terms

The search terms were taken from the WHO definition of palliative care.[10] From each dimension, a search term was identified, linked to a subject heading where possible, and used as a key word otherwise. The search terms were as follows:

- *Pain*—using the accepted palliative care definition that pain is what the patient says hurts;[11]
- *Symptoms*—representing physical problems from a patient-centered perspective. Self-reported symptoms have been shown to be more complete and clinically relevant than health provider (HP)-reported problems;[12]
- *Worry*—representing psychological problems. Worry is a symptom of all anxiety disorders[13] and is frequently associated with depression;[14]
- *Well-Being*—representing quality of life (QoL) and wish to live;
- *Support*—the family and informal caregivers are important aspects of palliative care. Social support in the literature is divided into two concepts: emotional and tangible/information support;
- *Peace*—the question "Are you at peace?" is a measure of spiritual well-being, validated

independently in palliative care populations in Uganda, South Africa,[15] and the U.S.;[16]
- *Information*—representing informational and tangible support, as distinct from emotional support.[17]

Each subject heading/key word was combined with "HIV seropositivity" using *AND*. Literature scoping showed that no key word or standard term was in use to describe the newly diagnosed population.

Inclusion and Exclusion Criteria

The inclusion criteria included the following: 1) original study (qualitative or quantitative) or review; 2) study of people with HIV (any country or group); 3) adults (18 years or older); 4) includes at least one of the seven problems; 5) English language; and 6) does not exclude newly diagnosed people, defined as those diagnosed within the previous six months.

Exclusion criteria included the following: 1) analysis group includes people diagnosed with HIV more than six months previously; 2) analysis group includes people who are HIV negative; 3) analysis group includes people who do not know they are HIV positive; 4) retrospective data collection; 5) false positive tests or HIV delusion; 6) full paper could not be retrieved, after attempt to contact authors; and 7) case study, editorial, or dissertation abstract.

The period of six months after HIV diagnosis was selected because it is a common exclusion criterion in observational studies and controlled trials,[18,19] showing that this group is viewed as being different from the average person with HIV.

All results were combined and cleaned. Abstracts were screened using the inclusion criteria, but retained if the abstract did not contain sufficient information to judge relevance. All remaining articles were read and those that passed the exclusion criteria were retained for review. Studies using retrospective data collection were not accepted for the systematic review, based on evidence from psychological studies that emotional events, such as HIV diagnosis, are remembered with heightened vividness and intensity but impaired accuracy.[20]

Analysis

Data were extracted into a standard proforma. Variables included authors, date of publication, setting, time from diagnosis to data collection, aim, study design, tools, analysis, and population. Findings were classified into the seven problems used as search terms. Results were compared within and between studies, but meta-analysis was not conducted because of the heterogeneity of samples and tools.

Secondary analysis was carried out by the review authors where appropriate and possible. For example, if only two data points of a cohort occurred within the six-month window, the results from these two points were compared using *t*-tests.

Study populations were classified using categories observed in scoping of the literature on recent diagnosis. Potential categories included recent seroconversion (SC); pregnancy; injection drug use; and hospital inpatients. Additionally, the countries where data collection took place were classified as low income, middle income or high income, using the World Bank classification system.[21] Results were tabulated by population group and by theme to compare both the prevalence of problems at HIV diagnosis in different populations and the development of the research base.

Results

Thirty-four studies were retained (Fig. 1). Fourteen were conducted in North America, 11 in Africa, three in Asia, three in Europe, and three in Central and South America (Table 1). According to the World Bank classification, 17 studies took place in high-income countries, seven in middle-income countries, and 10 in low-income countries.

Study Designs and Methodologies

Seven studies used patients' records for secondary analysis and 27 collected primary data. Two papers presented qualitative results,[22,23] and two collected data using in-depth interviews but presented findings quantitatively.[24,25] Study designs comprised 11 cohorts (usually with only two or three time points), eight observational cross-sectional studies, two case-control studies, one before-and-after trial, and one randomized

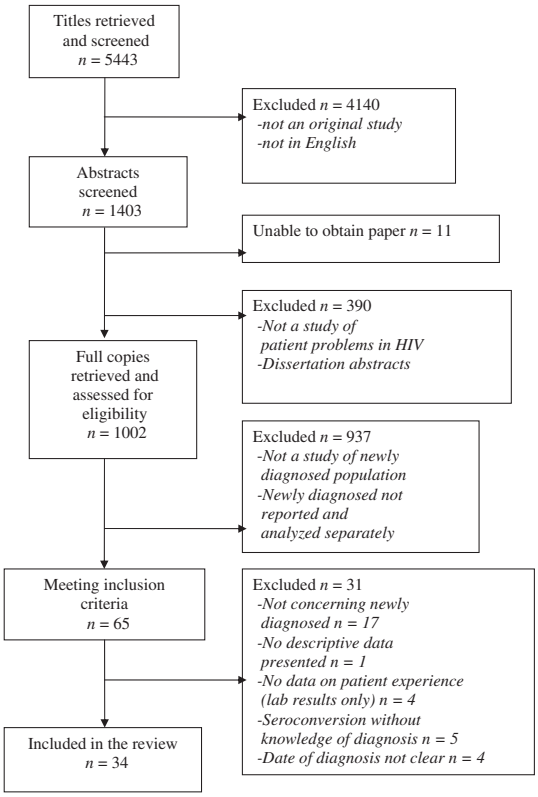

Fig. 1. Flow diagram of review process.

controlled trial (RCT). However, in many cases the primary research question, analysis, and design reported in the paper were not relevant to the review. In seven cohorts, only one measurement occurred within six months of diagnosis. For the purpose of the review, these data were presented as cross sectional. Similarly, only the baseline results from the RCT and before-and-after trial were reported.

Sixteen studies included a comparison or control group of people who were not newly diagnosed with HIV. The most common design (seven studies) was a prospective, unmatched, two-arm cohort, with a newly diagnosed HIV positive group compared with one that was HIV negative. The same comparison was used in a retrospective record review,[26] a cross-sectional survey,[27] a matched cohort,[28] and a matched case-control study.[29] Additionally, two cross-sectional surveys[30,31] and one prospective cohort[32] compared newly diagnosed participants with people with a pre-existing HIV diagnosis.

Two studies, a prospective cohort[33] and a case control,[34] compared newly diagnosed injection drug users (IDU) with newly diagnosed non-IDU. For these studies, results are presented separately for the two newly diagnosed groups.

When the outcomes were symptom prevalence or score on a validated instrument with clinical utility, such as the Beck Depression Index, then only the results from the newly diagnosed arm of the cohort are presented in the review. Results from control groups or study arms are only presented if they are needed to interpret the findings in the newly diagnosed group. For example, QoL instrument scores are essentially comparative.

Populations and Settings

Two case-control studies[29,34] and one two-arm cohort study,[33] all in high-income countries, recruited only patients with serological evidence of recent or current SC. Five studies in low-income countries[23,30,35–37] and three in the U.S.[24,28,38] recruited only pregnant women. Three studies took place in inpatient settings, all in low- and middle-income countries.[26,39,40] Three studies took place in low-income countries[41–43] and there were six studies of outpatients in middle-income countries.[27,44–47] Eleven studies were conducted in high-income countries. Six of them, all from the U.S., predated the introduction of highly active ART in 1996,[31,48–52] and five were conducted in the era of ART.[22,25,32,53,54]

Pain (11 Studies)

Table 2 displays the findings in the domains of pain and physical problems, by population group. In prospective observational studies, pain prevalence ranged from 31% to 53% in middle-income country outpatient populations,[46,55] and was 76% among low-income country patients with AIDS[41] and 69% for inpatients with herpes zoster.[39] In comparative studies, pain was not associated with HIV infection.[27,28] Two studies of SC compared prevalence of pain between IDU and non-IDU,[33,34] but the sample sizes were too small to draw any comparative conclusions. In qualitative interviews, patients with neuropathic pain described a three-stage process to manage pain. Neuropathic pain was exacerbated by its being outside previous experience and by the psychological and spiritual meanings attached.

Table 1

Results of Studies Retained in the Systematic Review of Palliative Care-Related Problems at HIV Diagnosis

Reference, Year, Country of Data Collection	Study Aim, Design, Sample Size, Tools	Population Type, Time from Diagnosis to Data Collection, Analysis	Findings: a) Pain, b) Physical, c) Psychological, d) Well-Being, e) Emotional Support, f) Spiritual, g) Information/Tangible Support
Akolo,[45] 2008, Nigeria	Aim: to determine the commonest symptoms and signs at presentation in HIV-infected individuals at a teaching hospital Design: cross-sectional prospective study of outpatients at HIV clinic ($n = 200$) Tools: a symptom checklist	Population: outpatients (middle-income countries) Time: "newly diagnosed"	b) 66% weight loss, 42% fever, 39% chronic cough, 32% diarrhea, 21% oral thrush, 20% wasting, 18% lymphadenopathy, 13% pruritus, and 13% body rash
Akpaka,[26] 2006, Jamaica	Aim: determine the prevalence of HIV infection in patients with pulmonary TB admitted to a hospital Design: retrospective study of patient's records ($n = 47$ HIV positive, $n = 359$ HIV negative)	Population: inpatients (middle-income countries) Time: diagnosed during current hospital stay	b) 89% fever, 89% weight loss, 47% dry cough, and 21% diarrhea
Alger,[38] 1993, USA	Aim: assess the influence of HIV infection on pregnancy outcomes and effect of pregnancy on short-term course of HIV infections Design: two-arm prospective cohort. Data for HIV positive arm during pregnancy presented only ($n = 101$)	Population: pregnancy (high-income countries) Time: diagnosed during current pregnancy	b) 28% genital candida, 13% condylomata, 12% oral herpes, 12% fatigue, 11% genital ulcers, 11% night sweats, 9% weight loss, and 5% genital herpes
Antelman,[35] 2007, Tanzania	Aim: examine the burden of depressive symptoms among HIV positive women in Tanzania ($n = 996$) Design: prospective cohort embedded in RCT (only one data point within six months of diagnosis) Tools: subscale of Hodgkins Symptom Checklist-25	Population: pregnancy (low-income countries) Time: mean 2.5 months after diagnosis	c) 43% depressed

Antoni,[51] 1991, USA	Aim: assess changes in psychological distress, plasma cortisol, and blastogenic responses following serostatus notification, to examine disparity between psychological and immune responses evident in HIV-positive individuals Design: prospective two-arm cohort of HIV positive ($n=25$) and HIV negative ($n=46$) gay men Tools: Impact of Events Scale (IES), State/Trait Anxiety Inventory (STAI), Profile of Mood States (POMS)	Population: outpatients (high-income countries) Time: two, three, and five weeks after diagnosis Analysis: means presented. Higher score = worse symptom	*Problem*	*Two weeks*	*Three weeks*	*Five weeks*
			c) STAI state anxiety	43.3	39.7	—
			POMS anxiety	14.8	11.7	11.9
			POMS depression	17.8	15.8	11.7
			IES intrusion	20.7	17.8	12.9
			IES avoidance	13.6	14.7	11.1
			IES total	34.3	32.5	24.0
Boyd,[53] 2005, U.K.	Aim: establish whether there are ethnic differences at HIV diagnosis in demographic characteristics, disease stage, and reasons for testing Design: retrospective study of patient's records ($n=494$)	Population: outpatients (high-income countries) Time: within three months after diagnosis	b) "Symptomatic:" 35% of whites, 30% black Africans, 25% black Caribbeans Tested because of symptoms: 19% of whites, 37% black Africans, 31% black Caribbeans			
Burchell,[29] 2003, Canada	Aim: understand the circumstances surrounding HIV testing among recent seroconverters ($n=80$) compared with HIV-negative controls Design: retrospective case control. Controls matched by gender, HIV exposure, and geographic region	Population: SC (high-income countries) Time: median three months since diagnosis	a) Of the 66% with symptomatic primary HIV infection (SPHI), 62% had severe headache b) 43% tested because of symptoms or illness, 8% because of sexually transmitted infection diagnosis Of the 66% ($n=53$) with SPHI, 100% had fever, 98% fatigue, 96% myalgia, 85% night sweats, 79% diarrhea, and 78% nausea			
Chandra,[46] 1998, India	Aim: study factors related to anxiety, depression, and suicidal ideation among HIV-positive heterosexuals soon after being tested for the first time Design: observational cross-sectional study ($n=51$) Tools: HADS	Population: outpatients (middle-income countries) Time: four to six weeks after diagnosis	a) 31% severe pain b) 55% painful symptoms c) 36% anxiety disorder, 40% depressive disorder d) 20% death wish, 12% occasional suicidal ideation, 8% attempted suicide e) 43% consider family indifferent, unsupportive, or hostile			

(*Continued*)

Table 1
Continued

Reference, Year, Country of Data Collection	Study Aim, Design, Sample Size, Tools	Population Type, Time from Diagnosis to Data Collection, Analysis	Findings: a) Pain, b) Physical, c) Psychological, d) Well-Being, e) Emotional Support, f) Spiritual, g) Information/Tangible Support			
Conley,[32] 1999, USA	Aim: evaluate the effectiveness of avoidance of serostatus information as a coping strategy by examining psychological well-being of gay men before and after they learned the results of an HIV test Design: secondary analysis of prospective two-arm before-and-after study. Only newly diagnosed results presented ($n=45$) Tools: POMS, Hopelessness Scale	Population: outpatients (high-income countries) Time: within six months of diagnosis Analysis: means presented. Higher score = worse result	*Problem* c) Concern about developing AIDS c) Subjective risk and lack of control c) Mood disturbance f) Hopelessness	*New diagnosis* 3.76 4.13 17.3 3.7	*Prior diagnosis* 3.55 3.97 29.9 4.5	*Notes* Max = 7 Max = 7
Davis,[52] 1995, USA	Aim: examine long-term changes in psychological symptomology from six to 24 months after notification of HIV-positive serostatus among IDUs Design: two-arm prospective cohort (HIV-positive IDU $n=16$, HIV negative IDU $n=81$). First data point presented only Tools: Symptom Checklist-90 (SCL-90), Beck Depression Inventory (BDI)	Population: outpatients (high-income countries) Time: within six months after diagnosis for 15 of 16 Analysis: means presented, *t*-tests by reviewer	b) SCL-90 c) BDI	*Positive* 58.6 15.4	*Negative* 60.0 13.5	*Test* $t=0.1$, $P=0.9$ $t=0.5$, $P=0.6$
Fitzgerald,[43] 2004, Haiti	Aim: determine whether information collected at HIV notification can predict patients' future adherence Design: retrospective study of patient's records ($n=1168$)	Population: outpatients (low-income countries) Time: on day of diagnosis	b) 26% recorded HIV symptom free c) Emotional reaction: 42% acceptance, 35% shock, 31% resigned, 16% sadness, 14% denial, 10% fear, and 5% tearful f) 2% angry			
Galati,[54] 2005, Italy	Aim: describe prevalence and determinants of HIV infection among low-risk subjects seeking their first test Design: retrospective study of patient's records ($n=64$)	Population: outpatients (high-income countries) Time: data collected during pre- or post-test counseling	b) 7% tested because of alarming symptoms			

Hult,[25] 2009, USA	Aim: describe the experience of testing positive for HIV Design: qualitative interviews ($n=50$)	Population: outpatients (high-income countries) Time: mean 6.7 weeks since diagnosis	b) 8% physical response to diagnosis (dry mouth, dizziness, sweating, cognitive impairment) c) 32% felt shock/surprise at diagnosis. 14% sadness, depression, or crying on diagnosis. 2% felt relief d) 4% felt suicidal e) 14% said health provider (HP) provided emotional support at diagnosis. 14% said HP's delivery of result was distressing. 10% said HP was very encouraging, and 10% said HP was upset
James,[24] 1988, USA	Aim: describe psychosocial problems encountered in patients referred for psychiatric evaluation during pregnancy following HIV diagnosis Design: retrospective study of patient's records ($n=15$)	Population: pregnancy (high-income countries) Time: 13 of 15 diagnosed during current pregnancy	c) 14 have psychiatric diagnosis (eight adjustment disorder, eight antisocial personality, six borderline personality, one dysthymia, one cyclothemia, one major depression, one R/O borderline intellect), three mood disorder, 11 unstable personality, 13 drug/alcohol abuse or dependence, and four attempted suicide before
Keogh,[37] 1994, Rwanda	Aim: describe specific HIV-related needs of a sample of HIV positive women and describe impact of HIV on their lives over a period of time Design: repeated in-depth qualitative interviews ($n=55$). Data from postdiagnosis interview only reported	Population: pregnancy (low-income countries) Time: at post-test counseling	c) 80% said HIV status caused a great deal of concern d) 94% glad to know their test result e) 24% thought partner would be supportive, 46% not sure. 35% said neither partner nor family would take in their children if they died g) 73% said relatives could not help with future HIV problems. 94% said no services available outside family. Current needs: 55% housing, 45% employment, 32% money, 30% childcare, 26% insurance, 23% food, 9% transport Most pressing need: 43% childcare
Kwalombota,[30] 2002, Zambia	Aim: investigate how pregnancy affects mental health and perceived QoL of HIV-positive women who receive diagnosis when already pregnant ($n=40$) and those already informed Design: two-arm prospective cross-sectional study Tools: a structured questionnaire	Population: pregnancy (low-income countries) Time: diagnosed during current pregnancy	c) 95% at least one somatic manifestation of anxiety, 25% poor concentration and lethargy d) 100% continuous suicidal thoughts, 95% lost interest in life, and felt worthless

(*Continued*)

Table 1
Continued

Reference, Year, Country of Data Collection	Study Aim, Design, Sample Size, Tools	Population Type, Time from Diagnosis to Data Collection, Analysis	Findings: a) Pain, b) Physical, c) Psychological, d) Well-Being, e) Emotional Support, f) Spiritual, g) Information/Tangible Support			
Larrabee,[28] 1996, USA	Aim: describe perceived QoL and functional status of women with HIV during the antenatal, perinatal, and postpartum periods Design: two-arm observational cohort. HIV-positive pregnant women ($n=21$) matched on age, race, parity, education to HIV-negative pregnant women ($n=21$). First data point only presented Tools: MOS-SF	Population: pregnancy (high-income countries) Time: diagnosed during current pregnancy Analysis: median scores presented, Wilcoxon signed-rank tests	*Problem*	*Positive*	*Negative*	*Test*
			a) Pain	66.6	66.6	$P>0.05$
			b) Physical function	77.8	83.3	$P>0.05$
			Fatigue	54.2	58.3	$P>0.05$
			c) Mental health	56.7	66.6	$P>0.05$
			Cognitive function	75.0	71.2	$P>0.05$
			d) Overall health	60.0	60.0	$P>0.05$
			QoL	60.0	80.0	$P>0.05$
			Health distress	50.0	87.5	$P<0.01$
			g) Role function	100	100	$P>0.05$
			Social function	100	66.6	$P>0.05$
MacNeil,[42] 1999, Tanzania	Aim: examine differences in sexual risk reduction among newly diagnosed people with HIV who receive care and support, compared with regular services Design: RCT of enhanced care and support services. Baseline data presented ($n=154$)	Population: outpatients (low-income countries) Time: four weeks after post-test counseling	b) 33% tested because of symptoms, 35% STD symptoms at baseline, and 23% genital sores e) 19% had disclosed at baseline			
Maman,[23] 2009, Democratic Republic of Congo	Aim: understand ways in which people living with HIV in Africa turn to religion for support Design: in-depth cross-sectional qualitative interviews, $n=40$	Population: pregnancy (low-income countries) Time: diagnosed during current pregnancy (those quoted)	e) Disclosing to church pastor initially helped to disclose to partner f) Women received support from religious beliefs and practices after HIV diagnosis			
Mansergh,[31] 1995, USA	Aim: to assess self-disclosure of HIV positive serostatus among asymptomatic and symptomatic men who vary in length of time since diagnosis Design: cross-sectional observational study. Results for newly diagnosed group presented ($n=79$)	Population: outpatients (high-income countries) Time: two to four months after diagnosis	b) 27% ($n=21$) self-reported "symptomatic" stage e) Symptomatic group: 100% disclosed status to lover (where relevant), 75% friend, 57% mother, 28% father, 43% sister, 39% brother, and 10% none of above Asymptomatic group: 75% disclosed to lover, 58% friend, 32% mother, 7% father, 28% sister, 19% brother, and 21% none of above			

Mientjes,[34] 1993, The Netherlands	Aim: study the clinical symptoms associated with HIV SC among IDU Design: case control. Cases were SC IDU ($n=18$), controls SC men who have sex with men (MSM) ($n=27$), HIV-negative IDU and long-term HIV positive IDU. Data presented for the two SC groups	Population: SC (high-income countries) Time: within six months after diagnosis	a) IDU: 11% pain with swallowing, 11% headache. MSM: 26% pain swallowing, 15% headache b) IDU: 22% tiredness, 33% fever, 11% night sweats, 28% bacterial pneumonia, 28% skin abscess. MSM: 30% tiredness, 48% fever, 19% night sweats
Montessori,[33] 2000, Canada	Aim: describe clinical and virological characteristics of acute/early HIV infection Design: two-arm prospective cohort study comparing newly diagnosed IDU ($n=33$) and non-IDU ($n=26$). Symptoms reported at baseline only	Population: SC (high-income countries) Time: within six months of SC	a) IDU: 58% headache. Non-IDU: 28% headache b) IDU: 65% pharyngitis, 50% lymphadenopathy, 81% fever, 58% rash, 73% anorexia, 54% diarrhea. Median symptoms 10 Non-IDU: 50% pharyngitis, 44% lymphadenopathy, 53% fever, 28% rash, 25% anorexia, 13% diarrhea. Median symptoms 4
Nuwagaba-Biribonwoha,[36] 2006, Uganda	Aim: study the effect of HIV infection on QoL during pregnancy and puerperium Design: two-arm prospective cohort study of HIV-positive ($n=132$) and HIV-negative women. HIV-positive arm results presented here Tools: Dartmouth COOP	Population: pregnancy (low-income counties) Time: 72% diagnosed during current pregnancy Analysis: "poor" = score 3/4 on 0–4 scale	a) 28% poor pain score b) 76% poor physical fitness score c) 12% poor feelings score d) 30% poor change in health score, 27% poor overall health score g) 36% poor social support score, 15% poor daily activities score, 9% poor social activities score
Olley,[27] 2008, Nigeria	Aim: examine association of QoL to negative life events, trauma, and sexual risk in HIV-positive patients in the air force ($n=56$) compared with HIV-negative air force personnel ($n=69$) Design: Comparative observational cross-sectional study Tools: MOS-HIV-30, Davidson Trauma Scale for post-traumatic stress disorder (PTSD)	Population: outpatients (middle-income countries) Time: recruited at diagnosis Analysis: mean scores presented, *t*-tests	*Problem* / *Positive* / *Negative* / *Test* a) Pain 0.4 0.4 $t=-0.3$, $P=0.8$ b) Physical function 7.4 6.3 $t=3.1$, $P<0.05$ c) PTSD 12.6 4.1 $t=5.1$, $P<0.01$ Mental function 11.6 8.2 $t=4.0$, $P<0.01$ d) Health perception 12.2 11.1 $t=1.6$, $P=0.2$ g) Role function 2.5 2.1 $t=2.7$, $P<0.01$ Social function 1.8 1.1 $t=2.6$, $P<0.05$

(*Continued*)

Table 1
Continued

Reference, Year, Country of Data Collection	Study Aim, Design, Sample Size, Tools	Population Type, Time from Diagnosis to Data Collection, Analysis	Findings: a) Pain, b) Physical, c) Psychological, d) Well-Being, e) Emotional Support, f) Spiritual, g) Information/Tangible Support
Ownby,[22] 2007, USA	Aim: explore everyday life experiences related to peripheral neuropathy in people with AIDS Design: in-depth qualitative interviews using grounded theory ($n = 19$ of whom at least three newly diagnosed)	Population: outpatients (high-income countries) Time: within six months after diagnosis for those quoted	a) Recognizing and rationalizing neuropathic pain f) Assimilating annoyance through seeking spiritual meaning in the pain Pain interpreted as punishment from God g) Modifying behavior, conserving energy, changing activities of daily living (ADL)
Perry,[50] 1990, USA	Aim: to determine the emotional impact of serological testing for HIV Design: prospective two-arm cohort. $n = 39$ HIV positive, $n = 179$ HIV negative Tools: Visual Assessment Scale (VAS), STAI, Brief Symptom Inventory (BSI), BDI, Hamilton Rating Depression Scale (HRDS)	Population: outpatients (high-income countries) Time: immediately (T0), two weeks (T1), and 10 weeks (T2) after diagnosis Analysis: *t*-tests comparing HIV positive to HIV negative at 10 weeks. Data presented for HIV-positive arm only	*Problem* / *T0* / *T1* / *T2* / *Test* c) VAS: mean Anxiety 65 43 34 Anxiety: $t = 2.2$, $P = 0.03$ Depression 42 27 24 Fear of AIDS 68 56 44 Fear of AIDS: $t = 2.9$, $P < 0.01$ Fear of infecting others 56 47 40 STAI 40.4 36.1 BSI 0.38 BDI 7.4 4.4 HDRS 6.6
Perry,[49] 1990, USA	Aim: to examine the effect of HIV testing on suicidal ideation Design: prospective two-arm cohort. $n = 49$ HIV positive Tools: BDI, Item 9	Population: outpatients (high-income countries) Time: one week after and two months after diagnosis Analysis: Chi-squared	*Problem* / *One week (n)* / *Two months (n)* / *Test* d) Suicidal thoughts Suicidal wishes 12 8 $\chi^2 = 1.01$ Suicidal intent 1 0 $P = 0.32$ 0 0
Perry,[48] 1993, USA	Aim: measure psychiatric effects of testing for HIV and assess what information feasibly available at intake might predict more severe psychiatric symptoms a year later Design: prospective two-arm cohort ($n = 106$ HIV positive) Tools: HRDS, BDI, BSI, STAI	Population: outpatients (high-income countries) Time: six months after diagnosis Analysis: second data point presented for HIV-positive arm only	c) 20% > 13 HRDS 18% > 13 BDI 16% > 10 BSI 31% > 45 STAI state anxiety 28% > 45 STAI trait anxiety 48% any of above

Sa,[44] 2007, Brazil	Aim: understand demographic and clinical profile of people presenting with HIV infection Design: retrospective chart review ($n=377$)	Population: outpatients (middle-income countries) Time: "the moment of diagnosis"	b) 47% asthenia, 44% cachexia, 32% fever, 31% anemia, 25% persistent dermatitis, 24% oral thrush, 17% diarrhea, 16% pulmonary TB, 13% persistent cough, 6% herpes zoster
Srisurapont,[47] 2001, Thailand	Aim: examine the impact of HIV-positive results on health related QoL and social support Design: observational prospective cohort ($n=30$ at Week 12, $n=27$ at Week 24) Tools: Social Relationship Scale (SRS), QoL Index (QL-Index)	Population: outpatients (middle-income countries) Time: 12 and 24 weeks postdiagnosis Analysis: means presented, *t*-tests conducted by reviewer	*Problem* / *12 weeks* / *24 weeks* / *Test* d) QL-Index: 9.80 / 9.74 / $t=0.27$, $P=0.79$ e) SRS-Q: 7.35 / 9.01 / $t=-1.02$, $P=0.31$ SRS-EN: 16.57 / 19.30 / $t=-0.75$, $P=0.46$
Strecker,[40] 1994, DRC (Zaire)	Aim: assess predictive value of WHO case definition for HIV Design: retrospective study of patient's records ($n=183$)	Population: inpatients (low-income countries) Time: diagnosed during current hospital stay	b) 70% weight loss, 36% diarrhea for >1 month, 53% fever, 25% cough and TB, 19% pruric dermatitis, 17% herpes zoster, 14% polylymphadenopathy, 5% oral candidiasis
Tyndall,[39] 1995, Kenya	Aim: determine clinical features, degree of immunosuppression, and prevalence of HIV associated with herpes zoster Design: prospective observational study ($n=196$)	Population: inpatients (low-income countries) Time: diagnosis within a week for 193 of 196	a) 69% severe pain b) 57% fever, 14% cough, 9% rash other than zoster, 8% weight loss, 6% diarrhea, 2% oral thrush
Wakeham,[41] 2010, Uganda	Aim: measure symptom burden prior to starting ART in adults presenting for HIV care with CD4 < 200 ($n=212$) Design: cross-sectional survey as part of double-blinded RCT Tools: Memorial Symptom Assessment Scale-Short Form	Population: outpatients (low-income countries) Time: "at the time of initial HIV testing and diagnosis"	a) 76% pain b) 70% weight loss, 67% itching, 61% drowsy/tired, 61% lack of energy, 57% numbness/tingling in hands/feet, 53% cough, 52% skin changes, 49% lack of appetite, 43% dizziness, 42% problems with sexual interest/activity c) 51% worry, 47% feeling sad g) 46% hunger
Wig,[55] 2008, India	Aim: describe multidimensional health-related issues of HIV positive patients Design: cross-sectional study with convenience sampling, $n=138$ Tools: a new questionnaire	Population: outpatients (middle-income countries) Time: within two weeks after diagnosis	a) 53% problems due to pain, 44% suffering due to body pain b) 96% lack of energy, 40% active TB, 22% oral candidiasis, 20% persistent diarrhea c) 99% emotional problems d) 92% problems related to health perception, 68% unhappy most of the time f) 58% not feeling calm and peaceful, a source of high distress g) 54% problems with job or household work

Table 2

Findings in the Domains of Pain and Physical Problems, Tabulated by Population Group in Which Problems Were Recorded

Domain	SC (High-Income Countries)	Inpatients (Low-Income Countries)	Inpatients (Middle-Income Countries)	Outpatients (Low-Income Countries)	Outpatients (Middle-Income Countries)	Outpatients (High-Income Countries)	Pregnant (Low-Income Countries)	Pregnant (High-Income Countries)
Pain	IDU: 11%–58% headache Non-IDU: 15%–62% headache	69% severe pain (comorbid herpes zoster)		76% of patients with AIDS	31%–53% Low pain in air force, not associated with HIV	Rationalizing and seeking meaning in neuropathic pain	28% poor pain score (=severe pain)	Pain not associated with HIV
Physical	IDU: 73% anorexia 65% pharyngitis 33%–81% fever 58% rash 54% diarrhea 22% tiredness Non-IDU: 48%–66% fever 30%–65% tiredness 51% nausea 50% pharyngitis 19%–56% night sweats 13%–52% diarrhea 28% rash 25% anorexia 43% tested because of symptoms	53%–57% fever 67% itching 8%–70% weight loss 25% active TB 14% cough 6%–36% diarrhea 9%–19% skin problems 2%–5% oral thrush	89% fever 89% weight loss 47% cough 21% diarrhea	70% weight loss 67% itching 61% tiredness 53% cough 52% skin problems 49% cachexia 35% STD symptoms 74% “symptomatic” 33% tested because of symptoms	47%–96% tiredness 66% weight loss 55% “painful symptoms” 44% cachexia 32%–42% fever 13%–39% cough 13%–25% skin problems 16%–40% active TB 17%–32% diarrhea 21%–24% oral thrush 27% “symptomatic” 7% tested because of symptoms Lower physical function associated with HIV status	8% had physical response to diagnosis 19% of whites and 37% of black Africans “symptomatic” Symptoms burden not associated with HIV for IDU	76% poor physical fitness	41% female problems 12%–41% low energy 28% difficulty eating 28% genital thrush 25% vision problems 13% condylomata 12% oral herpes 11% night sweats 9% weight loss Physical function and fatigue not associated with HIV

Physical (22 Studies)

Physical symptoms were highly prevalent in the general population of low- and middle-income countries. Prevalence information from high-income countries was confined to pregnant women or recent seroconverters. Common symptoms included tiredness (47%–96%), weight loss (66%–70%), fever (32%–42%), and skin problems (13%–52%).

Weight loss, fever, cough, and diarrhea were the four most common symptoms in four low- and middle-income country prevalence studies.[26,39,40,45] For people with AIDS in Uganda, the most prevalent symptoms were weight loss, itching, tiredness, and lack of energy.[41] High frequencies of sexually transmitted infection (STI) symptoms also were noted among newly diagnosed participants in Tanzania.[42] In India, 96% of a convenience sample reported lack of energy, 40% tuberculosis (TB), and 20% diarrhea.[55] In Brazil, the most common symptoms were asthenia, cachexia, fever, and anemia, but TB, diarrhea, and cough were recorded for more than 10% of patients.[44]

Pregnant women in the U.S. reported fatigue, night sweats, and weight loss, and a number of STIs, not necessarily symptomatic.[38] Pregnant women in Uganda, using the Dartmouth COOP scale, reported a poor physical fitness score in 76% of cases.[36]

In comparative findings, HIV positive IDU in Canada reported more symptoms than HIV-positive non-IDU, suggesting that drug use had more effect than HIV on symptom burden.[33] By contrast, in the Netherlands, non-IDU had higher symptom burden for fever and tiredness at SC.[34]

The only information on physical symptoms in high-income countries, apart from patients experiencing either SC or pregnancy, was derived indirectly from asking patients their reason for taking an HIV test. In Italy, 7% of people with HIV from "low-risk" groups reported testing because of "alarming symptoms."[54] Forty-three percent of recent seroconverters in Canada took an HIV test because of symptoms or illness,[29] compared with 33% of the HIV-positive population in Tanzania.[42] In the U.K., patient's records showed that 37% of black Africans and 19% of whites tested HIV positive after symptoms.[53] Finally, learning of a positive HIV diagnosis could itself be a cause of symptoms. In the U.S., 8% of respondents reported a physical reaction such as sweating, dry mouth, and dizziness.[25]

Psychological (17 Studies)

Table 3 has only five columns rather than the eight in Table 2, because no results in any of the nonphysical domains (i.e., psychological, well-being, spiritual, emotional, or informational/tangible support) were found for inpatients in low-income and middle-income countries or recent seroconverters.

For low-income country outpatients, anxiety and depression prevalence were high (51%–95% and 47%, respectively). In middle-income countries, anxiety and depression were less prevalent but still high, and 99% of an Indian sample reported emotional problems.[55] In the U.S., 28% scored above the study case-defining threshold in terms of trait anxiety and 18% for depression.[48]

Two studies with outlier results were methodologically weak, one problematically translating "emotional health" to "feelings" and then to "mental state,"[36] and the other failing to describe any instrument or symptom checklist.[30]

Four comparative studies used psychological measures. The largest, in Nigeria, found post-traumatic stress disorder and lowered mental health were associated with HIV.[27] In the three smaller studies, all in the U.S., HIV status was not associated with mental health.[28,32,52]

Qualitative interviews in the U.S. revealed the primary response to diagnosis to be shock, sadness, and depression.[25] In Haiti, reactions were shock, resignation, sadness, denial, and fear.[43] Prevalence of anxiety, depression, intrusive thoughts, and fear appeared to decline over time in two American cohorts,[50,51] although statistical analysis was inappropriate.

Well-Being (10 Studies)

This was constructed using various outcomes including problems relating to health perception, unhappiness,[55] poor overall health,[36] attempted suicide,[46] and thoughts of suicide.[25,30] Cohort studies did not identify a significant change in well-being over time.[47,49]

Emotional Support (Eight Studies)

Family reaction is a particular concern, with lack of support expected,[37] indifference and

Table 3

Findings in the Five Domains of Nonphysical Problems, Tabulated by Population Group in Which Problems Were Recorded

Domain	Outpatients (Low-Income Countries)	Outpatients (Middle-Income Countries)	Outpatients (High-Income Countries)	Pregnant (Low-Income Countries)	Pregnant (High-Income Countries)
Psychological	47% depressed 51%–95% worried 42% responded to diagnosis with acceptance, 35% shock, 31% resignation, 16% sadness, 14% denial	36% worried 40% depressed 99% emotional problems PTSD and low mental function associated with HIV	18%–20% depression, 32% say primary response was shock, 14% sadness Anxiety, depression and fear decline over five- to 10-week period Depression not associated with HIV	80% say HIV status causes a great deal of concern 12% low feelings score	41% problems thinking, 41% risk of depression Comorbidities include AD, ASPD, BPD Mental health, cognitive function, and depression not associated with HIV
Well-being		8% attempted suicide 12% suicidal ideation 20% death wish 68% unhappy most of the time 92% problems related to health perception QoL does not change between 12 and 24 weeks after diagnosis Health perception not associated with HIV	4% felt suicidal at diagnosis 24% suicidal thoughts after one week 16% suicidal thoughts after two months	100% suicidal thoughts 95% lost interest in life 27% poor overall health 30% poor change in health 94% glad to know their test result	Mean perception of health is average Overall health and QoL lower in HIV-positive group but not associated with HIV
Emotional support	19% had disclosed status after four weeks	43% consider family unsupportive, hostile, or indifferent Social relationship quality does not change from 12 to 24 weeks after diagnosis	14% say HP provided emotional support 14% say HP added to distress Men with symptoms are more likely to disclose their status	Disclosing to pastor helped women disclose to their partner 24% think partner would be supportive 46% not sure whether partner would be supportive 35% say family/partner would not take their children in if they died	
Peace	2% angry at diagnosis	58% highly distressed by not being calm or peaceful	Seeking spiritual meaning in pain to assimilate annoyances	Women receive support from religious beliefs and practices	
Information/tangible support	46% of people with AIDS report hunger	54% report problems with household or work HIV associated with more limited role function and social function	Modifying behavior, conserving energy, changing ADL to reduce neuropathic pain	73% said relatives could not help with future HIV problems. Current needs: 55% housing, 45% employment, 32% money, 30% childcare, 23% food Most pressing need: 43% childcare 36% poor social support, 15% poor daily activities, 9% poor social activities	19% have limited physical function in walking uphill 16% limited at work 6% limited ADL Role function and social function not significantly associated with HIV

hostility experienced,[46] and resulting lack of disclosure among those with less advanced illness.[31] Qualitative evidence suggested that spiritual support aided disclosure.[23]

Spiritual (Four Studies)

Not feeling calm and peaceful was a source of high distress,[55] and further studies investigated hopelessness[32] and anger.[43] Spiritual care providers gave effective assistance in managing shock, sadness, and anger at diagnosis, and also mediated acceptance of diagnosis by the patient and family.[23] Inner spiritual resources also assist the newly diagnosed to interpret and manage neuropathic pain.[22]

Information/Tangible Support (Seven Studies)

In many contexts, people with HIV were restricted in their work, activities, and social support. There was limited evidence of association from comparative methods.

Problems included lack of awareness of any support services outside the family;[37] need for housing, employment, and child care;[37] problems with their job or doing household work;[55] hunger;[41] and limitations to role function and social function.[27]

Discussion

Importance of Palliative Care at Diagnosis

The findings demonstrate a high prevalence of problems across all palliative care dimensions within six months of HIV diagnosis. Diagnosis is a particularly important time for intervention, for several reasons. First, WHO[5,56] and UNAIDS[4] policies stipulate that HIV palliative care should begin at diagnosis. Second, palliative care is patient centered, and from the perspective of the patients, diagnosis, rather than infection, is the beginning of the disease. Third, palliative care incorporates prevention of suffering and its relief; therefore, quality HIV palliative care should be delivered as early as possible to maximize this opportunity. Finally, there is an increasing concern regarding loss to follow-up of newly diagnosed patients who do not return for care until their disease is far advanced.[57,58] The physical symptoms, worry and depression, loss of well-being and sense of meaning, and limited practical support identified in this review might prevent patients from remaining in care. Palliative care may improve patient retention because of its total care approach and focus on patient experience.

Situating Findings in the Literature

The accepted view of the adverse emotional and psychological effects of an HIV diagnosis[48,59,60] appears to have a poor evidence base. The best evidence of the impact of diagnosis came from a study almost 20 years old, with a total sample of only 69,[51] which found high anxiety, depression, and intrusive thoughts a week after HIV diagnosis. It seems that, to date, the newly diagnosed have been thought to have a high psychological burden, but the multidimensional nature of their needs has been unexplored. The necessity for a multidimensional approach is reflected in a study that found many newly diagnosed people "had a host of social, emotional, and informational needs, which often seriously impeded their capacity to make constructive use of the knowledge of their HIV status."[61] Taking an HIV test is stressful in itself. Anxiety, distress, depression, and suicidal ideation are highly prevalent at testing, independent of HIV status.[49,62]

Gaps in the Evidence

The majority of evidence concerned physical and psychological symptoms. Evidence of need for emotional support was largely represented by studies of disclosure, which is related to prevention of further infections and is not necessarily patient centered. Almost no quantitative research was actively directed at understanding spiritual distress, while qualitative papers explained that the topic was raised by participants and had not formed part of the interview schedule. Only three studies recruited outpatients in low-income countries and yet the majority of HIV diagnoses probably occur in this setting. Theories of psychological adjustment and coping suggest that problems may change rapidly[63] and, therefore, longitudinal studies are important. Although 11 of the 34 studies used a cohort design, only four collected data more than once within six months of diagnosis.[47,49–51]

The data on problems of inpatients and problems of recent seroconverters related only to physical symptoms and pain. The prevalence of physical symptoms was very high in these groups and it seems likely that

psychological, spiritual, and social problems also would have caused burden, but there has been no research in these areas.

Quality of Evidence

Many studies had methodological problems. Ten reported symptom prevalence using records completed by care providers rather than patients. Provider-completed patients' records have been shown to underestimate symptoms reported by patients.[12,64] The time period within which symptoms were reported was rarely given. No information on symptom severity, duration, or distress was recorded in any studies, nor was any association drawn between symptoms and QoL. Most studies focused on only one area of care and did not aim to measure multidimensional need.

The categories "symptomatic" and "asymptomatic" were used,[31,43,53] which are derived from the surveillance definition of HIV, not the clinical definition.[65–67] This classification distinguished between HIV infection with and without case-defining symptoms, but regressed into general and inaccurate use of the word "asymptomatic" to describe pre-AIDS HIV.[68,69]

Several studies did not describe data collection methods in adequate detail. The instruments used, such as the Memorial Symptom Assessment Scale-Short Form, the Hospital Anxiety and Depression Scale (HADS), and the Medical Outcome Study-Short Form, had frequently not been validated and piloted in the population and setting where they were used, or else symptom prevalence information was presented without specification of an instrument.[29,38] Sample sizes were small in most prospective studies. The nature of questions was not always clear. For example, when participants were asked what their most pressing problem was, it was not clear whether they picked an option from a closed list or recorded open answers.[37] It was not always possible to interpret study findings in terms of clinical significance.

The four longitudinal studies to have more than one point within the range of the review suffered from several methodological flaws. The use of only two time points did not allow for exploration of the rate of change over time. The analysis techniques used were limited to unpaired *t*-tests and Chi-squared tests. These tests assume independence between measurements and do not account for the clustering effect within individuals.

Limitations of the Review

It was not always clear when data collection had taken place in relation to diagnosis. For example, retrospective studies of hospital records were sometimes included because, logistically, diagnosis could only have taken place between admission and discharge, but the paper did not draw attention to this point.[26]

The epidemiological, cultural, and social environment has not been considered in any depth. Because of the small number of papers, and heterogeneity of settings, outcomes, and samples, all studies were presented together with no subgroup comparisons. Other studies set comorbidity conditions, such as TB,[26] herpes zoster,[39] and peripheral neuropathy,[22] and one included only patients with a CD4 count below 200.[41] In these cases, the results are only generalizable to similar groups.

Despite considerable effort, some studies could not be obtained because they were published in small regional journals with very limited access. Because of shortage of time and resources, papers were limited to the English language. Publication bias may have distorted the findings of the review. However, the review used a broad search strategy and followed established guidance.[9]

Conclusion

At HIV diagnosis, patients have a range of distressing but manageable problems, including pain, worry and depression, social concerns, spiritual distress, lack of information, and impaired well-being. There is evidence that HIV palliative care can be effective in the domains of pain, symptoms, anxiety, insight, and spiritual well-being.[2] Better outcomes can be achieved and patient's retention in care may be improved. It is clear from the literature that many HIV symptoms and problems are not identified by clinicians,[64] and from our review that multidimensional problems are present from the point of diagnosis. Therefore, from diagnosis onward, quality HIV care must include assessment of multidimensional problems, an integrated palliative care approach to management, and

referral to specialist palliative care for complex problems, alongside ART. At the same time, patient centeredness must be a principle of HIV clinical research to identify and solve the problems that are most important to patients.

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